2014

Evaluation of the Allometric Exponents in Prediction of Human Drug Clearance

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EVALUATION OF THE ALLOMETRIC EXPONENTS IN PREDICTION OF HUMAN DRUG CLEARANCE

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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August, 2014

ACKNOWLEDGEMENTS

First and foremost, I would like to sincerely thank my advisor, Dr. F. Douglas Boudinot, for giving me the opportunity to pursue graduate studies under his guidance and for his continuous professional support, guidance, encouragement and patience throughout my graduate program. He was always delighted in sharing his vast knowledge and kind warmth. I would also like to thank Dr. Ahmad for his scientific advice and support through the completion of my degree. He has been a kind and helpful mentor for me. I would like to acknowledge my graduate committee members, Drs. Susanna Wu-Pong, Patricia W. Slattum, Phillip M. Gerk and Alaa Ahmad for their advice, time for serving on my committee as well as their timely guidance and input.

My parents, Defen Zheng and Yuliang Zhang, my sister, Lei Zhang and other family members for their unconditional love and support.

Last, but not least, my husband, Huadong, and sons, Albert and Daniel for their understanding and love during these years. Their unwavering patience and encouragement was crucial for the successful completion of my part-time Ph.D.

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LIST OF ABBREVIATIONS

Abbreviation	Interpretation
%IONI	ionization status
AAFE	average absolute fold-error
AFE	average fold-error
ANOVA	one way analysis of variance
AS	allometric scaling
AUC	area under the curve
BMR	basal metabolic rate
BrW	brain weight
CL	clearance
clogD	calculated logarithm of the octanol-water distribution coefficient
clogP	calculated logarithm of the octanol-water partition coefficient
CNSa	central nervous system absorption
CWRES	conditional weighted residuals
df	degree of freedom
DMPK	drug metabolism and pharmacokinetics
ELIM	elimination pathway
elogD	estimated logarithm of the octanol-water distribution coefficient at pH 7.0 based on HPLC assay

EPS (□)	residual variability
EST	estimation ($ESTIMATION)
ETA (□)	empirical Bayes prediction of the inter-drug random effect
fixed effects	population parameters assumed to be constant each time data is collected
FO	first-order approximation
FOCE	first-order conditional estimation
FOCEI	first-order conditional estimation with interaction
HBA	hydrogen bond acceptor count
HBD	hydrogen bond donor count
IDV	inter-drug variability
IPRED	individual predicted value based on individual's ETAs
LBF	liver blood flow
LL-LR	log-log transformation followed by linear regression
MEM	mixed effect modeling
MLP	maximum lifespan potential
MW	molecular weight
NLS	nonlinear regression methods
non-H	number of non-hydrogen atom
OFV	objective function value

OrlA	oral absorption property
Papp	apparent permeability through cell membrane
PGPh	human P-glycoprotein transporting property
PGPr	rat P-glycoprotein transporting property
PK	pharmacokinetics
PPB	plasma protein binding
PRED	population prediction
PSA	polar surface area
QSAR	quantitative structure–activity relationship models
random effects	sample-dependent random variables
RCB	rotatable carbon bond
RMSE	root mean square error
ROE	rule of exponents
RSE	relative standard errors
W	body weight

ABSTRACT

EVALUATION OF THE ALLOMETRIC EXPONENTS IN PREDICTION OF HUMAN DRUG CLEARANCE

By Da Zhang, M.S.

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2014.

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Background. Allometric scaling (AS) is widely used in predicting human clearance (CL) based on animal data. Substantial prediction errors have been commonly observed and various

modifications to AS have not provided a broad reliable improvement. In this study, an extensive data set was assembled including animal and human systemic CL and physiochemical properties. The allometric exponents were calculated based on multiple species AS and single-species AS methods. The correlations between the allometic exponents and physiochemical properties were evaluated in an attempt to find covariates that may explain the inter-compound variability in the allometric exponents. Lastly, the statistical approaches in analyzing the allometric function were evaluated with the collected data.

Methods. 1- A nonlinear mixed effect modeling (MEM) approach was performed to investigate the central tendency and distribution of AS exponents as well as to identify whether there are any correlations between the allometric exponent, and coefficient, with the physicochemical and drug metabolism and pharmacokinetics (DMPK) properties of the compounds. 2- Single-species AS was performed to estimate the single-species AS exponent distributions and their corresponding central tendencies. The correlation between the estimated single-species AS exponents and the physicochemical and DMPK properties of the compounds were also examined. 3- The methodologies of log-log transformation followed by linear regression (LL-LR) and direct nonlinear regression methods (NLS) with different weighting schemes on the AS power function were investigated. The central tendency and distribution of the allometric exponents were evaluated and compared across methods. Furthermore, the human CL prediction performance was evaluated among methods.

Results. The estimated central tendency and distribution of AS exponents from the nonlinear MEM as well as the single-species AS approaches were consistent with literature reports. There were no significant correlations identified between the estimated AS exponents and the physicochemical or DMPK properties. The methods of LL-LR and the NLS with $1/w^2$ weighting

(variance weighted by CL^2 during the variance minimization process) results in the most similar allometric exponent with central tendency around 0.668 and provided the best human CL prediction among methods investigated.

Conclusion. The knowledge gained in this work by extensive modeling and simulations contributed to a better understanding of the variability in AS exponents and better practice in performing AS in human CL prediction

CHAPTER 1

INTRODUCTION

Research on allometric scaling (AS) was introduced to biology about one century ago (1). AS was developed based on the principle that the relationship between organ size, regional perfusion and body weight of mammals could be characterized by a simple mathematical power law expression, $Y = a\ (\text{body weight})^b$, where Y is the parameter of interest, and a and b are the allometric coefficient and exponent, respectively. The observed power function is empirical, although there is some possible underlying physiological rational (2). In 1970, Dedrick and coworkers published the first paper to apply the concept of allometic analysis to drug disposition (3). The AS concept was fully developed and applied to the field of pharmacokinetics by Boxenbaum in the early 1980s (4). Since then, AS has been widely used in predicting human pharmacokinetic parameters, including drug CL based on *in vivo* animal pharmacokinetic data. However, it has been frequently reported that the simple body-weight based AS method using *in vivo* data from the common preclinical animal species fails to accurately predict human pharmacokinetics (5).

Over the years, great effort has been focused on how to improve the accuracy of AS. Various modified allometrically based scaling methods with correction factors, both empirical and

mechanistic in nature, have been proposed (6). Lave et al. proposed *in vitro* correction methods using hepatocyte data to normalize the *in vivo* CLs, which led to lower median deviation between the observed and the predicted CLs in man (7). Boxenbaum proposed a two-term power function approach (4). By scaling unbound CL, Feng et al. have shown an improved prediction for low CL compounds with extraction ratios of 0.3 or less (8). Boxenbaum suggested the incorporation of maximum lifespan potential (MLP) as a correction factor to normalize the metabolic capacity across species (4). Mahmood and Balian proposed using brain weight (BrW) as a correction factor to improve the prediction performance of the empirical AS method. Later, Mahmood proposed the rule of exponents (ROE) (9) which states that if the exponent from simple AS is between 0.55 and 0.70, simple AS is applied, if the exponent is between 0.70 and 1.0, the CL × MLP is applied and if the exponent is greater than 1.0, CL × BrW is applied (9). ROE is based on empirical observations, which suggest that when a large exponent is observed, it is likely that human CL based on animal data will be over-predicted. The MLP or BrW correction is thus utilized to correct the potential over-prediction (9). Recently, Tang et al. proposed an empirical model that provided better predictability for human CL than ROE by introducing the intercept concept and correcting for plasma binding differences between animals and humans (10). Other various approaches have been suggested to improve AS for compounds eliminated through renal or biliary excretion, or metabolism (11).

However, the applications of these correction factors in allometry have been controversial. The correction using *in vitro* metabolic data was successful in predicting human CL for ten extensively metabolized drugs (7). However, due to the small size of the dataset, whether such a correction method could improve the prediction for other compounds remains unknown. Feng at al. demonstrated by scaling unbound CL, there was a certain degree of success for improving the

prediction for low CL compounds, however, the method failed to adequately predict CL for other compounds illustrating large vertical AS such as diazepam and valproate (8). The vertical AS refers to the situation where human CL was largely over-predicted by performing AS (12). Corrections based on MLP or BrW also demonstrate some success, but the number of examples is limited (13). Moreover, if used indiscriminately, these two approaches may worsen the prediction for certain compounds. This limitation led to the proposal referred to as ROE (13). ROE proposes selection criteria for the use of a MLP or BrW correction based on the values of exponents obtained from simple AS. However, due to the artificial cutoff of the exponent values and the small sample size (n = 38), it remains unknown on whether the ROE rule is generally applicable to other drugs. More recent studies by Nagilla and Ward demonstrated that the correction using MLP/BrW or the ROE in AS did not result in improvements in prediction of human CL. At the same time, the same authors proposed that a correction factor using monkey liver blood flow (LBF) provides better prediction than ROE (14). The LBF method for prediction of human clearance can be expressed in each of the preclinical species as a fraction of liver blood flow as follows: human clearance = animal clearance • (human liver blood flow/animal liver blood flow) (15). Additionally, Tang and Mayersohn pointed out that there is an intrinsic defect in using correction factors or ROE. Their work indicated that applying correction factors in AS was found to be equivalent to applying certain constant values that are predetermined on the basis of the species chosen and these correction factors bear no relationship to values of CL in the animals (16).

Another major inconsistency or controversy in AS is whether to use varying-exponent allometry or fixed-exponent allometry (17). AS extrapolation based on the empirical power function whose exponent and coefficient is estimated from animal species is termed as varying

exponent AS, which includes the simple AS and AS with any modifications and correction factors described above. The limitations and intrinsic defects of this approach have been extensively discussed (14). Currently, fixed-exponent AS is commonly used in the pharmaceutical industry. This approach includes data from one or two species (18) and any other general models having fixed exponents in the AS function. As noted in a recent publication by Tang et al, varying-exponent AS is not recommended. Various correction methods on the traditional AS should not be used as well (19). It has been postulated that the physicochemical properties of a compound may influence the success/failure of interspecies extrapolation. Individualization of the AS exponent based on the physicochemical factors of a certain category of compounds might be a promising direction.

One common criticism of AS is its empiricism, which is heavily dependent on the data selection and sample size. Generally AS methods have been developed based on relatively small sets of data (13). Inconsistency and controversies among different allometric methods or models were partially due to the limited data sets that have been analyzed. In this study, one of the major goals was to collect an extensive and diverse animal and human systemic CL data set, using multiple approaches to systemically investigate allometric exponents and their further application for human CL prediction.

This study included the largest allometric data set collected from the literature, with a total of 251 drugs with systemic CL values in humans and rat or dog or monkey. Their corresponding physiochemical and certain drug metabolism and pharmacokinetic (DMPK) properties were also estimated.

There are three major aims in this study. The first primary aim of this study was to investigate the potential correlations between the allometric exponents from multiple-species AS method and the physiochemical properties, with an attempt to identify covariates that may explain the inter-drug variability in AS relationship, thus enabling individualization of AS for better human CL prediction. A nonlinear mixed effect modeling (MEM) approach was applied to investigate the central tendency and distribution of AS exponents, as well as to identify whether there are any correlations between the allometric exponent/coefficient and the physicochemical and DMPK properties. Nonlinear MEM analysis is a one-stage approach, which simultaneously considers the population samples, rather than at the individual level, as a unit of analysis for the estimation of the distribution of parameters, sources of variability, as well as their relationship with covariates within the population. Overall, with the largest data set reported in the allometric field of pharmacokinetics and the rigorous analyses on the correlations of the physiochemical properties and allometric relationship, this work could demonstrate the impact of physiochemical covariates on the allometric predictions of clearance.

The second aim of this study was to evaluate the commonly used single species AS using the same data set. The estimated single species AS exponents were compared with generally accepted single species AS exponents. The correlations between the estimated AS exponents and the physicochemical or DMPK properties of the compounds were investigated. In addition, the uncertainties of the exponents of the single species methods obtained from this study were valuable as they provide a framework in incorporating the parameter uncertainty in predicting human CL using single species, which is highly recommended in real practice.

The last aim of this study was to evaluate the statistical methodologies in analyzing allometric functions, namely the log-log transformation followed by linear regression (LL-LR) and direct

nonlinear regression (NLS) with different weighting schemes. The log-log transformation of both sides of the empirical power function followed by linear regression (LL-LR) is the widely used approach when AS is adopted for human CL prediction. However, it should be noted that there is no theoretical basis for LL-LR being the most appropriate way to present the AS relationship and there is no prior knowledge that CL must follow a log-normal distribution in the allometric model (19). In this study, direct application of nonlinear regression with different weighting strategies was performed for the power function and the resulting exponents were compared to the LL-LR method. In addition, the prediction performance of direct nonlinear regression methods was compared to that of LL-LR method. Furthermore, the statistic indices, root mean square error (RMSE%) and BIAS%, which have not been evaluated in the allometric field, were assessed on its predictability in predicting human CL. Lastly, LL-LR analysis corrected by maximum life-span potential (MLP) and brain weight (BrW), which have been proposed and used by some researchers, were also being compared with the direct LL-LR method for human CL prediction.

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CHAPTER 2

IMPLEMENTATION OF NON-LINEAR MIXED EFFECT MODELING APPROACH IN ALLOMETRIC SCALING FOR HUMAN CLEARANCE PREDICTION

1_Abstract

Objective: Investigate whether there are any correlations between the allometric exponent, as well as the allometric coefficient, and the physicochemical properties and pharmacokinetics (DMPK) of different compounds based on an extensive scientific review of the literature.

Methods: After mining the scientific literature, a total of 251 literature reported drugs with intravenous pharmacokinetic parameter (CL) values in humans and rat or dog or monkey (at least three species including humans) were collected and were used as the MEM model dataset. The physicochemical and DMPK properties of each drug were estimated. The nonlinear MEM modeling approach with NONMEM was applied to the data to investigate the central tendency and distribution of allometric scaling (AS) coefficient and exponent. An investigation was conducted between the AS exponent and coefficient (CL at unit weight) with the physicochemical and DMPK properties of drugs to identify potential significant covariates.

Results: A nonlinear MEM AS model with additive residual error was developed. The estimated central tendency and distribution of AS exponent was consistent with literature reports. Polar surface area (PSA) was identified as statistical significant covariate for AS coefficient by explanation of 5.7% of inter-drug variability for AS coefficient from 104% to 98.3%. However, compared to the 98.3% remained un-explained inter-drug variability (IDV), this 5.7% IDV finding may not have much practical usage.

Conclusion: By using MEM modeling for allometric scaling, the central tendency and distribution of AS exponent was systemically investigated and confirmed the empirical adopted value. None of the physicochemical and DMPK properties investigated were found to significantly affect the prediction of human CL by AS.

2_Introduction

Allometric Scaling

In drug discovery, accurate human pharmacokinetic parameters prediction, particularly clearance (CL) is essential not only to project efficacious first-in-man doses but also facilitate in predicting appropriate dosing frequency and safety margin as well as obtaining insights into differentiation of available clinical candidates (1). Various methods have been proposed and applied over the past decades to predict human CL, such as scaling from *in vitro* human tissue or *in vitro* animal data, *in vivo* interspecies scaling and physiologically based pharmacokinetic modeling (2-8). As one of the most widely used approaches, allometric scaling (AS) has been explored for the prediction of human drug clearance (CL) based on the measure values of CL in animal species (9).

AS was developed based on the principle that the relationship between organ size, regional perfusion and body weight of mammals could be characterized by a simple mathematical power expression, $Y = a\ W^b$, where Y is the parameter of interest, W is body weight and a and b are the allometric coefficient and exponent, respectively. Because of the empirical nature of AS, it has been frequently reported that the simple body-weight based AS method using *in vivo* data from the common preclinical animal species fails to accurately predict human pharmacokinetics (10). Over the years, numerous modifications have been proposed to improve the AS prediction capacity (11)(12). Lave et al. proposed *in vitro* correction methods using hepatocyte data to normalize the *in vivo* CL, which led to lower median deviation between the observed and the predicted CL in man (13). By scaling unbound CL, Feng et al. showed an improved prediction for low CL compounds with extraction ratios of 0.3 or less (14). Boxenbaum suggested the incorporation of maximum lifespan potential (MLP) as a correction factor to normalize the

metabolic capacity across species (15). Mahmood and Balian proposed using brain weight (BrW) as a correction factor to improve the prediction performance of the empirical AS method. Later, Mahmood proposed the rule of exponents (ROE) (16). Recently, Tang et al. developed an empirical model that provided better predictability for human CL than ROE by introducing the intercept concept and correcting for plasma protein binding differences between animals and humans (17). Other various approaches have been suggested to improve AS for compounds eliminated through renal or biliary excretion, or metabolism (18-22).

However, the applications of these correction factors in allometry have been controversial. The correction using *in vitro* metabolic data was successful in predicting human CL for ten extensively metabolized drugs (13). However, due to the small size of the dataset, whether such a correction method could improve the prediction for other compounds remains unclear. Feng et al. demonstrated that by scaling unbound CL, there was a certain degree of success for improving the prediction for low CL compounds with extraction ratios of 0.3 or less (14). However, the method failed to adequately predict CL for other compounds illustrating large vertical AS such as diazepam and valproate. The vertical AS refers to the situation that human CL was largely over-predicted by performing AS (23). Corrections base on MLP or BrW also demonstrated some success, but the number of examples is limited (24). Moreover, if used indiscriminately, these two approaches may worsen the prediction for certain compounds. This limitation led to the proposal referred to as ROE (16). ROE proposes selection criteria for the use of a MLP or BrW correction based on the values of exponents obtained from simple AS. However, due to the artificial cutoff of the exponent values and the small sample size (n = 38), further investigation on whether the ROE rule is generally applicable to other drugs is needed. More recent studies by Nagilla and Ward demonstrated that the correction using MLP/BrW or

the ROE in AS did not result in improvements in prediction of human CL (20)(25)(26). Additionally, Tang and Mayersohn pointed out that there is an intrinsic defect in using correction factors or ROE (27). Their work indicated that applying correction factors in AS was equivalent to applying certain constant values that are predetermined on the basis of the species chosen and these correction factors bear no relationship to values of CL in the animals.

It has been postulated that the physicochemical properties of a molecule may have an important impact on its pharmacokinetic fate in the body. Therefore, we hypothesized that physicochemical properties of drugs could influence the success of interspecies extrapolation. Individualization of the AS exponent based on the physicochemical factors of a certain category of compounds could be a promising direction.

The Nonlinear MEM Analysis

Nonlinear mixed effect modeling (MEM) analysis is a one stage approach, which simultaneously considers the population samples, rather than at the individual level, as a unit of analysis for the estimation of the distribution of parameters and their relationship with covariates within the population. The word "mixed" refers that the method simultaneously evaluates both fixed (such as covariate effect etc.) and random effects (such as inter-drug variability and intra-drug variability etc.).

In population pharmacokinetics, the MEM approach is ideally suited for analyzing data from large clinical trials, where only a few samples are available for each subject (28). This technique identifies individual-specific characteristics that impact the disposition of a drug. In addition, the results are more generalizable than those of the traditional methodology because a greater number of subjects are evaluated (29).

In this study, an exhaustive literature search was conducted and an extensive database of intravenous drug CLs in different species was compiled. The physicochemical properties of each collected compound were estimated. With this large and diverse database, using the population nonlinear mixed effect modeling (MEM) analysis, the potential impact of physicochemical and drug metabolism and pharmacokinetics (DMPK) properties on AS exponents as well as the coefficient (CL per unit body weight) were investigated. Any significant and meaningful correlations between the allometric exponent and other characteristics of the drugs, if found, are expected to greatly improve the predictions of CL, since the exponent for each drug may be individualized to best represent the allometric relationship between animals and humans.

3_ Materials and Methods

Data collection

Two hundred and fifty one sets of intravenous administered drug CL data were collected from the literature (**Table 1.**). For each selected drug, there are at least three animal species CL values (rat, dog, monkey and human). The CL values included in the database were systemic clearance determined following intravenous drug administration. This data collection was initiated based on a few major review and/or research papers on AS (Obach, Ward, Tang et al.) (30)(31). Also a general search with key words such as "allometric scaling", "allometry PK prediction", etc. were performed on PubMed to capture some individual reports that were not included in the review papers. During the data searching and assembling process, the original literature reporting CL values for each individual drug across species were revisited and evaluated to ensure the quality of the data collection, including the following major considerations and efforts. The first effort was to ensure the pharmacokinetic calculations of CL. For example, CL should be calculated from the parent compound data, as a few limited papers may have reported the CL calculated from the total radioactivity. For another example, the CL calculation should be based on the area under the curve (AUC) infinity or steady-state AUC. If these two AUCs were not reported and used for CL calculations, an examination was given to the time-concentration profile to make sure the AUC extrapolated should be a minor contribution to the AUC infinity. The second effort was around the PK linearity. PK in animals (occasionally) and PK in humans (many times) were done at multiple doses. If there were indications of nonlinear PK, the CL in animals and humans were selected based on the values obtained at allometrically comparable doses across species. The term of "allometric comparable" means the doses after scaling by the body weights with an allometric exponents roughly at 0.67. For example, an 1 mg/kg dose in rats was approximately

comparable to 0.15 mg/kg dose in humans. The third effort was mainly given to the examinations of human PK on a numbers of important factors, such as human population, co-medications, etc. Generally the CL values should be obtained from the healthy animal populations, as animal PK was generally done in healthy population. Also most CL values were obtained from the studies with single drug administrations. In cases of studies with co-medications, assessment was made, based on general DMPK properties of the drug of interest, that there was no significant DDI involved. For certain instances, there were multiple reports (for example, PK from single ascending doses and multiple ascending doses were available) for the same compound, a weighted average was estimated taking into the consideration of the study size. Some additional efforts were made by digitalizing the original plots and re-analyze the PK data when there were apparent mismatches or questions between the PK parameters and time-concentration profiles with DigitizeIt version 2.0.0 (available at http://digitizeit.soft112.com/) and Phoenix version 1.3 (Certara L.P. Cary, North Carolina).

Physicochemical and DMPK Properties Estimation

The two-dimensional physicochemical and topological descriptors of the collected compounds were computed with a proprietary program (Chemoinformatics, Monika Five v 1.2, Merck), which predicts physicochemical and ADME properties based on chemical structures. After an initial screening, a total of 17 physicochemical and drug metabolism and pharmacokinetics (DMPK) properties of drugs were selected for MEM modeling. The physicochemical and DMPK properties of drugs were: 1) molecular weight (MW); 2) hydrogen bond acceptor count (HBA); 3) hydrogen bond donor count (HBD); 4) number of non-hydrogen atoms (nonH); 5) polar surface area (PSA); 6) rotatable carbon bond (RCB); 7) calculated logarithm of the octanol-water partition coefficient (cLogP); 8) estimated logarithm of the

octanol-water partition coefficient at pH 7.0 based on HPLC assay (elogD); 9) calculated logarithm of the octanol-water distribution coefficient at pH 7.4 (clogD); 10) ionization status (%IONI); 11) oral absorption property (good, moderate, bad)(OrlA); 12) plasma protein binding (PPB); 13) central nervous system absorption (CNSa); 14) apparent permeability through cell membrane (Papp); 15) human P-glycoprotein transporting property (PGPh); 16) rat P-glycoprotein transporting property (PGPr); and 17) elimination pathway (ELIM). These terms are defined and discussed below.

The molecular weight was calculated as the mean natural isotope weight of the compound. The hydrogen bond acceptor count and hydrogen bond donor were computed by substructure search. The number of non-hydrogen atom represents the non-hydrogen atom count. The polar surface area demonstrates the topological polar surface area according to Ertl et.al (32). The rotatable carbon bond represents the single bond between heavy atoms that are both not in a ring and not terminal. The logP is a widely used measurement of the lipophilicity of a compound and therefore an important physico-chemical parameter in relation to its pharmacological behavior, such as membrane permeation and plasma protein binding. The calculated logP (clogP) was the calculated partition coefficient of the neutral form of the compound in octanol/water based on the proprietary logP calculation system (Biotyte). The estimated logD (elogD) was evaluated at pH 7.0 based on high-throughput HPLC assay. The clogD represents the calculated logarithm of octanol /water distribution coefficient at pH 7.4. The ionization status indicates the percentage of the molecule will be ionized at the given reference pH and is derived from the individual pKa values of ionizable groups in the molecule. The oral absorption characteristics was predicted based on a new *in silico* classification model, which was derived from the classic Lipinski Rule of 5 (33). The plasma protein binding was classified based on the measurement of how much of a

given compound is bound to plasma proteins versus how much is free in solution. Central nervous system absorption was classified based on 6 relevant calculated properties - MW, clogP, H-acceptors, H-donors, PSA and Rotatable bonds - with respect to how well the compound is likely to pass the blood-brain barrier (BBB)(34). The apparent permeation through the cell membrane was calculated using a random forest quantitative structure–activity relationship models (QSAR models). The apparent Human and rat P-glycoprotein (PGP) transport properties, measured in an uM assay and calculated by a random forest QSAR model. This model, based on human or rat PGP data expressed as BA: AB ratios, tried to predict the actual value of the BA:AB ratio. Being collected from the literature reports, the elimination pathway was characterized as by metabolism or excretion or by both. The compounds that are only excreted unchanged through kidney or bile are categorized to be "excretion". The compounds metabolized before renal or biliary excretion are considered under "metabolism" type. For the compounds that have percentage of metabolism and excretion are categorized to be "both".

MEM Modeling Approach on AS

The relationship between the AS parameters and the above mentioned physicochemical characteristics was investigated using the population nonlinear MEM modeling approach based on the literature collected pharmacokinetic data following intravenous drug administration. For each drug, there were CL values in at least 3 species (rat, dog, monkey and human). This population-based method was evaluated to provide a more reliable AS exponent and coefficient central tendency and distribution estimation, examine the within-drug and between-drug variability, as well as identify both statistically significant and practically meaningful covariates (physiochemical and DMPK properties) on the AS exponent or coefficient. Statistically and practically significant covariates may be expected to improve the predictions of CL, since the

exponent for each drug may be individualized to best represent the allometric relationship between animals and humans.

The population MEM analysis of AS on the combined data set was performed by using NONMEM® (version VII, Icon Corp, Hanover, MD)(35). Several estimation methods (first-order approximation (FO), first-order conditional estimation (FOCE) and first-order conditional estimation with interaction (FOCEI)) were explored. Compared to FO method, the FOCEI method can provide less biased results. During the preliminary modeling exploration, the FOCEI approach did converge smoothly. Therefore, the FOCEI method was chosen as the estimation method and was employed for all model runs. The maximum likelihood ratio test was used to discriminate between alternative models. An objective function value (OFV) decrease of 3.84, 6.64 and 10.83 units were considered significant for $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively (χ^2 degree of freedom (df) = 1).

Basic structure model of AS

By adopting the commonly used approach for AS, the basic structural model of the AS function was written as:

$$\text{Log}\,(CL_{ij}) = \log\,(a_i) + b_i \times \log\,(W_{ij}) \quad (1)$$

In Eq. (1), CL_{ij} is the CL for jth species in ith drug, W_{ij} is the body weight for jth species in ith drug, and a_i is the allometic coefficient (intercept of the log-log transformation followed by linear regression (LL-LR) equation) and b_i is the allometric exponent (slope of the LL-LR equation) for ith drug.

Inter-drug variability

In this model component, the individual drug parameter estimates were modeled as a function of typical value for the population and individual random deviations. Inter-drug variability was assumed to be normally distributed with mean zero and variance of ω_a^2 and ω_b^2 for allometric coefficient and exponent, respectively. The inter-drug variability of the MEM model parameters were explored for each one of the functions listed below Eq. (2), take the allometric exponent (coded as the SLOP in the basic structure model) as an example:

Exponential: $SLOP = TVSLOP \times e^{\eta_{slop}}$

Additive: $SLOP = TVSLOP + \eta_{slop}$

Proportional: $SLOP = TVSLOP \times (1 + \eta_{slop})$ (2)

Where, TVSLOP is the typical value of the allometric exponent for the drug population; SLOP is the individual parameter estimate; η_{slop} is the inter-drug variability term on SLOP, representing the difference between the individual parameter estimate and the population mean. The exponential function was selected after initial exploration for inter-drug variability of the allometric SLOP and coefficient. Non-diagonal entries for ηs were assumed to be zero.

Intra-drug variability

The difference between the predicted CL and observed CL is defined as residual variability, which is comprised of but not limited to intra-drug variability, experimental error, and bio-analytical analysis error and/or model misspecifications. It was modeled using additive, proportional and combined error structure as described below Eq. (3):

Additive error: $CL_{ij} = \hat{CL}_{ij} + \varepsilon_{ij}$

Proportional error: $CL_{ij} = \widehat{CL}_{ij}(1+\varepsilon_{ij})$

Combined additive and proportional error: $CL_{ij} = \widehat{CL}_{ij}(1+\varepsilon_{ij}) + \varepsilon_{ij}'$ (3)

Where CL_{ij} was the jth observed CL in the ith drug, $\widehat{CL}_{ij}$ was the corresponding model predicted CL, and ε_{ij} (or ε_{ij}') was a normally distributed random error with a mean of zero and a variance of σ^2. Based on the goodness of fit, the additive error function was selected for the description of intra-drug variability in this investigation.

Covariate model development

A core objective of this MEM modeling approach investigation on the AS relationship was to identify the sources of variability from the physicochemical and DMPK properties of drugs which could significantly affect the AS exponent and coefficient estimation. Quantitative assessment of the relationship between covariates and AS exponent and coefficient is important for drug development because it could potentially provide critical information on categorized AS exponent values for different drug categories, then assist in more accurate human CL prediction.

Covariate identification and its selection criteria - The effect of an individual drug's specific physicochemical and drug metabolism and pharmacokinetics (DMPK) properties, cLogP, molecular weight, polar surface area, clogD and others were tested on AS parameters during the covariate model development. The covariate models were developed by a forward inclusion / backward elimination using the maximum likelihood ratio test criteria. For the forward inclusion stage, covariates that were significant at the 0.01 level were retained in the model (χ^2, ΔOFV = -6.64, df = 1). Once all the covariates that are significant at the 0.01 level have been included in the model, a backward elimination process was conducted. A significant level of 0.001 was used

for the backward elimination (ΔOFV = -10.83, df = 1). The backward elimination process was repeated until all remaining covariates were significant ($p<0.001$). Covariate influence on inter-drug variability and goodness of fit were also evaluated. Covariate factors should also have clinical or practical relevance.

Incorporation of covariates **-** The covariates can usually be classified as continuous covariates such as cLogP and molecular weight and discrete covariates including oral absorption property, elimination pathway and others. These two types of covariates were incorporated into the model as described below Eq. (4) (5). Take the allometric exponent (coded as the SLOP in the basic structure model) as an example:

The incorporation of a continuous covariate for the AS exponent (SLOP)

$$TVSLOP = \theta_{SLOP} \times (Cov / Med_{Cov})^{\theta_{Cov}}$$

$$SLOP = TVSLOP \times e^{\eta_{\text{slop}}} \qquad (4)$$

Where TVSLOP is the population estimate of the AS exponent for an individual drug having a specific covariate; θ_{SLOP} is the population estimate for AS exponent without a covariate effect; Cov is the continuous covariate that is affecting AS exponent; θ_{Cov} is the constant describing the association between covariate and typical value of parameter estimates; and Med_{Cov} is the median value of Cov; SLOP is the individual estimate of AS exponent, which is the population estimate for AS exponent incorporating the covariate and inter-individual drug variability; η_{slop} is the inter-individual variability term for AS exponent.

The incorporation of a discrete covariate involves assigning a numeric value to the covariate (e.g. oral absorption property, low = 1, moderate = 2, high = 3). The incorporation of this covariate is shown below:

IF (oral absorption property.EQ.1): TVSLOP= θ_{low}

IF (oral absorption property.EQ.2): TVSLOP = $\theta_{moderate}$

IF (oral absorption property.EQ.3): TVSLOP = θ_{high}

Model evaluation

The aim of model evaluation was to determine whether the model is a good description of the original data set. The model evaluation methods in this project are listed below.

Assessment of Goodness-of-fit

Graphical inspection of model predictions versus observations was performed through all steps of model development to assess the diagnostic plots for model goodness-of-fit. Diagnostic plots include observed CLs versus population prediction (PRED), observed CLs versus individual prediction (IPRED), conditional weighted residuals (CWRES) versus PRED, and CWRES versus log (WT). Model stability inspection was also conducted through all model steps for conditional number, which was defined as the ratio of the largest Eigen value to the smallest Eigen value and was calculated using the PRINT=E option on the $COV in the NONMEM control stream (ideally be $\leq|1000|$, as a condition number exceeding 1000 is indicative of ill-conditioning of the model). Additionally, the final developed model was also evaluated using a bootstrap technique (resampling with replacement), as suggested by Efron (36).

Statistical Assessment for Prediction Performance

The predictability of the nonlinear MEM model on AS for individual drug CL was assessed by average fold-error (AFE) and the average absolute fold-error (AAFE)(37):

$$\text{Fold-error} = \frac{CL_{predicted}}{CL_{observed}}$$

$$\text{AFE} = 10^{\frac{\sum \log(\text{fold-error})}{\text{N}}}$$

$$\text{AAFE} = 10^{\frac{\sum |\log(\text{fold-error})|}{\text{N}}}$$

AAFE and AFE are measures of precision and bias of the overall prediction, respectively. In the equations, N represents the total number of drugs in the database. AFE representing the geometric mean of fold-errors allows the measurement of overall bias in both directions. As a result, AFE less than or greater than 1 indicates an overall under or over-prediction, respectively. The closer to 1, the better precision AAFE demonstrates.

4_Results

A total of 251 drugs with literature reported CL values in humans and rat or dog or monkey were collected and were used as the MEM model dataset. The final database with the literature collected CL values in all species, the estimated physicochemical and DMPK properties, and literature reported elimination pathway information is shown in **Table 1.** The compounds compiled in this study encompass a wide variety of structures, and span a broad range of fundamental physicochemical properties and therapeutic usage. For human CL, the data span over a considerable range from 0.0037 to 1070 ml/min, however, approximately 80% of human

CL values of the compounds resided in the range of 1 and 10 ml/min. Among the 251 drug data base, 137 drugs are primarily metabolized, 91 drugs are eliminated by renal or biliary excretion and 23 drugs are eliminated by both pathways.

Basic Structure Model

The basic structure model parameter estimates are shown in **Table 2.** The AS exponent was estimated to be 0.629 (% Relative Standard Errors (RSE) = 2.93) with inter-drug variability (IIV) estimated to be 41.3% and the AS coefficient as estimated to be 2.06 (%RSE = 7.80) and the IIV to be 104%.

Final Covariate Model

The key challenge of building a covariate model is over-parameterization, which could lead to convergence difficulties and covariance step failures. When two or more potential covariates are highly correlated, the best recommended strategy is to select a reduced set of covariates that have the greatest scientific plausibility to reduce co-linearity among continuous covariates. Therefore, in this study, for the 17 physicochemical and DMPK properties estimated for each compound, correlations among those physicochemical and DMPK properties across the drug population were performed to avoid over-parameterization during covariate modeling. As a result, hydrogen bond acceptor count (HBA), hydrogen bond donor count (HBD) and number of non-hydrogen atom (nonH) were found to be closely related to molecular weight (MW). Therefore, only molecular weight was kept in the data set to represent the chemical size character of the corresponding compound. A similar high correlation was identified between human P-glycoprotein transporting property (PGPh) and rat P-glycoprotein transporting property (PGPr). Human P-glycoprotein transporting property (PGPh) was thereafter chosen to be kept in the data

set to represent the P-glycoprotein transportation properties. At the same time, the calculated and the estimated logarithm of octanol /water partition coefficient both represent the lipophilicity of a compound and therefore only the estimated logP value was chosen in the main data set. As a result, a total of twelve physicochemical and DMPK properties were kept for further covariate modeling. Statistics and the distributions of the calculated physicochemical and DMPK properties which were used for the final model development are shown in **Table 3.** and **Figure 1.**

The covariate modeling started with graphical exploration for potential relationships between final basic structure model parameters and each potential covariate, scatter plots of inter-drug variability of the AS exponent and coefficient from basic structure model (ETAs) versus continuous covariates and box plots of ETAs versus categorical covariates were investigated (**Appendix 1.**). As a result of the graphical exploration, no apparent correlations were identified for any pair of ETAs versus potential covariates. However, there were weak trends identified between the AS coefficient and PSA, RotB, PGPh and ELIM as well as AS exponent with clogP, Papp, Ppb, PGPh, Psa, RotB and ELIM being identified. Therefore, during the final covariate model development, these potential covariates were introduced to each parameter one by one by power or exponential functions. Based on the covariate modeling strategy described in the method section, after forward addition procedures, the combination of PSA + RotB was identified to be a significant covariates for AS coefficient and Ppb was identified to be significant covariate for AS exponent. Following backward elimination steps, PSA was identified to be the statistically significant covariate of AS coefficient by resulting in a drop in OFV by 23.6 points ($p < 0.001$). The final model parameter estimations are shown in **Table 2.** The AS exponent was estimated to be 0.628 (%RSE = 2.94) with inter-drug variability (IDV)

estimated to be 41.3% (%RSE = 29.2). The AS coefficient as estimated to be 2.08 (%RSE = 7.44) and the IIV to be 98.3%.

With the consideration of the covariate effect from PSA, the inter-drug variability of the AS coefficient dropped from the base model of 104% to the final model at 98.3% , which means PSA helped explain about 5.7% of the inter-drug variability on AS coefficient. From a practical perspective, this provides no significant improvement for the explanation of AS coefficient variability. The covariate effect from PSA on AS coefficient did not help to reduce inter-drug variability of AS exponent, which was kept constant from the basic structure model to the final model at 41.3% (%RSE = 29.2). The estimates of shrinkage for inter-drug variability on AS exponent and coefficient were all under 5% and the shrinkage for residual variability was high for both base and final models, which was caused by fixing residual variability. During initial modeling process, both IDV and residual variability was open for estimatio, the IDV estimation was not stable with big shrinkage. After an initial exploration of a range of different residual variability, the 18% residual variability was selected for both base and final based on the model stability, shrinkage for residual variability and reasonably estimation of inter-drug variability.

The evaluation of the final AS nonlinear MEM model was done by assessment of goodness of fit (GOF) in **Figure 2**. The observed CL values agreed well with the final model predicted CL values. The conditional weighted residuals did not reflect any systematic trends, suggesting that the final model accurately reflects the data. From the plots (A) and (D) in **Figure 2**, phencyclidine which has the smallest PSA in the data set (PSA = 3 Å) demonstrated a different population prediction versus observation correlation compared to other drugs in the plots. This is because, compared to basic structure model (GOF plots not shown), PSA was selected to be a significant covariate on AS coefficient and had been included in the final model. Case deletion

test was therefore performed on phencyclidine by repeatedly modeling the basic structure model and final covariate model with and without phencyclidine. As a result, phencyclidine did not test to be a significant outlier. The conclusion of PSA as a statistical significant covariate had not been influenced by including and excluding phencyclidine from the data set. Therefore, phencyclidine was kept in the data set for continuing AS modeling and simulation purposes.

The distribution of observed human CLs (Plot a. and b. in part 1) as well as the final model predicted human CL distribution (Plot c. and d. in part 2) for compounds in this study are illustrated in **Figure 3.** The log transformed observed or predicted CLs illustrated that human CLs follow a log normal distribution. A similar central tendency and distribution on log-transformed human CLs was identified between the final AS model prediction and the observation, which demonstrated the final model did a fairly good prediction of human CLs.

The robustness of the basic structure model and the final covariate model were also assessed with the nonparametric bootstrap procedure (**Table 2)**. Of the 1000 replicates for both the basic structure model and the final model, 100% converged successfully, indicating good model stability. The median parameters obtained from bootstrap replicates for both base and final models were similar to the NONMEM model estimates and the parameters appeared to be reasonably well estimated. Based on the final AS model, the individual drug fits of the observed versus model predicted CLs across species and drugs in this data set were demonstrated in **Appendix 2**. For most of the drugs in the data set, the AS final model predictions did capture the observed CLs well.

In this study, AFE and AAFE were calculated to examine the prediction capacity of the final model. The AFE value was estimated to be 1.12, which indicates a slight overestimate, but a

fairly good prediction. The AAFE was calculated to be 1.41, which demonstrates a relatively good precision for the CLs prediction. The final model estimated AS exponents based on the diverse data base were also investigated. The central tendency (median = 0.663) and the distribution of the model predicted AS exponents were very similar to the literature review results by Hu et al (38). The comparison is shown in **Figure 4.**

5_Discussion

In this study, CL values for humans and rat or dog or monkey were collected from the literature. This diverse database forms a unique basis for the investigation of AS for human CL prediction through a nonlinear MEM approach aiming to get a deeper understanding of the relationship between commonly investigated drug physicochemical and DMPK properties and pharmacokinetic fate of drugs in the body.

Physicochemical properties and their impact on drug pharmacokinetics and metabolism is a broad and complicated topic. There are no simple and unifying indicators which can explain the processes of drug metabolism and excretion. Over the years, quite a few groups of researchers have investigated the relationship of DMPK and drug physicochemical properties(39)(40). However, no relationship has been identified between CL and any chemical structure characteristics. Most of these studies have been conducted in a direct correlation level with limitations due to relatively small data set sizes.

As a major part of this study, a nonlinear MEM model of AS for human CL prediction was developed. The final model demonstrates a fairly good capture of the observed CL values in different species across a diverse drug population. The central tendency of the AS exponent

estimated out of this modeling project confirmed the empirical AS exponent value generally used in the AS field and has provided a solid evidence for further usage. No practically meaningful covariate was identified for the AS exponent. For the AS coefficient, the small IIV variability on AS coefficient that has been explained by PSA is not at a practically meaningful level for drug development.

The population analysis, nonlinear MEM approach, is a powerful tool superior to various traditional analysis methods in certain aspects. It is a one stage approach by considering the population samples (rather than the individual) as a unit for the estimation of the distribution and central tendency of parameters, variability and their relationship with covariates within the population. In this study, with the advanced modeling approach, there was still no significant covariate identified for the AS exponent (out of the 12 physicochemical and DMPK properties estimated for the compounds in the database). This result may indicate that most likely there are indeed no correlations between those physicochemical and DMPK properties and CL allometric exponent values. Lipophilic drugs are usually eliminated by liver metabolism followed by biliary excretion or by active excretion by transporters. For this type of compound, drug CL is a series of biochemical processes and may depend more on the functionalities of drug transporters and metabolic enzymes rather than the drug chemical structures. For most hydrophilic drugs, such as those antibiotics with logP values small than 0, passive renal excretion is usually the elimination route, which follows well the allometric law for the flow parameters (41). Most drugs studied here or in the current discovery/development pipeline, are more lipophilic, so metabolic elimination dominates, therefore, physiochemical properties may not be the major factors in determining the interspecies difference and thus may not be able to explain the variability in

allometric exponents. On the other hand, volume of distribution may have a greater dependence on the physicochemical properties of a drug (42).

For a future direction, in order to get good human CL predictions for compounds under development, a better understanding of the drug metabolic pathway and possible transporters across species, might improve human CL prediction.

Table 1. Drug clearance values in different species with physicochemical and DMPK properties

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	Elog D	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	Clog P	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	Clog D	%IONI (0-100%)	ELIM	Ref
Acecainide (N-acetylprocainamide)	280	9.24	76.8	---	0.94	0.73	21	2.5	38	1.7	Good	1.6	277.4	3	2	61	7	20	-0.6	99.6	excr	(30) (43)
Acetaminophen	350	4.95	48	36.5	0.98	-0.4	33	0.55	58	0.58	Good	0.5	151.2	2	2	49	1	11	0.5	0	metab	(30) (44)
Acivicin	48.3	2.112	16.8	11.5	0.92	0.17	3.9	0.58	28	0.91	Bad	-1.6	178.6	5	2	85	2	11	-4.1	100	excr	(30) (45)
Actisomide	475.3	15.84	144	100	0.94	2.9	30	1.5	93	1.2	Moderate	5.4	369.5	4	0	36	6	27	2.6	99.9	both	(30) (46) (47)
Acyclovir	329	2.211	73.2	44	1	-0.45	8.1	0.68	25	0.68	Bad	-2.4	225.2	6	3	115	4	16	-2.4	1	excr	(30) (48)
Adefovir	259	7.26	63.6	80	0.83	0.53	4.2	0.82	25	1	Bad	-1.9	273.2	8	3	146	5	18	-5.8	100	excr	(30) (49)
Albuterol (salbutamol)	546	32.01	384	---	0.55	-1.6	10	0.93	23	0.96	Moderate	0.1	239.3	4	4	73	5	17	-2.2	---	excr	(30) (50)
Alfentanil	273	9.57	228	160	0.99	2.1	25	4.2	79	2.8	Good	2.1	416.5	6	0	81	9	30	1.8	67	metab	(30) (51)
Almotriptan	623	18.414	342.24	200	0.96	1.7	31	2.6	63	1.3	Good	1.8	335.5	3	1	56	6	23	-0.1	99.2	excr	(30) (52)
Amifloxacin	319.2	3.96	54	36.5	0.23	0.098	8.4	2.2	47	1.5	Good	1.4	334.4	7	2	76	3	24	0.4	100	excr	(30) (53)
Amikacin	77	1.782	42	---	0	1.4	1.9	4.2	42	3.7	Bad	-6.3	585.6	17	13	332	10	40	-11.6	100	excr	(30) (54)
Aminocyclopropanecarboxylic Acid	105	1.056	4.8	15.5	0.97	1.1	3.5	0.66	23	0.7	Bad	-3.4	101.1	3	2	63	1	7	-5.9	100	excr	(30) (55)
Amiodarone	133	8.25	348	---	0.33	3.1	17	2.7	99.4	1.5	Bad	8.9	645.3	3	0	43	11	31	7	99	metab	(30) (56)
Amlodipine	490	40.26	132	---	0.62	2.1	11	4.9	85	2.5	Good	3.4	408.9	7	2	100	10	28	1.9	97	metab	(30) (57)
Amoxicillin	231	5.61	40.8	---	0	-0.18	3.1	3	62	2.1	Bad	-1.9	365.4	7	4	133	4	25	-5.3	100	excr	(30) (58)
Amphetamine (-d)	679	29.7	85.2	---	1	0.76	24	0.56	56	0.68	Good	1.7	135.2	1	1	26	2	10	-0.7	99.7	both	(30) (59)
AmphotericinB	11.9	0.627	10.8	21	0.08	2.7	3.2	5.8	87	5.3	Bad	-0.6	924.1	17	11	299	3	65	-3.2	100	excr	(30) (60)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Ampicillin	196	6.27	109.2	---	0	0.29	3.7	1.8	51	1.8	Bad	-1.2	349.4	6	3	113	4	24	-4.7	100	excr	(30) (61)
Amsacrine	301	27.39	192	---	0.85	2.6	28	3.8	99.1	2.1	Good	4.7	393.5	5	2	80	5	28	4.6	68	metab	(30) (62)
Amsalog	182	21.78	44.4	---	0.58	2.4	20	6.4	98	3.8	Good	4.5	464.5	6	3	109	6	33	4.5	8	metab	(30) (63)
Antipyrine	44.8	3.003	75.6	23	1	1.1	43	0.54	81	0.56	Good	0.2	188.2	2	0	24	1	14	0.2	0	metab	(30) (64)
Aprepitant	70	5.94	31.2	---	0.88	3.5	26	6	98	2.6	Moderate	4.8	534.4	6	2	75	8	37	4.8	0	metab	(30) (65)
Artesunate	74900	69.96	528	---	0.72	1.5	7.5	0.96	93	1	Good	2.9	384.4	8	1	101	5	27	-0.1	99.9	metab	(30) (66)
Atenolol	175	22.77	52.8	37.5	0.72	0.54	7.7	2.6	29	1.3	Good	-0.1	266.3	4	3	85	8	19	-2.1	99.1	excr	(30) (67)
Atomoxetine	651	11.88	88.8	---	0.99	2.1	32	0.92	95	0.97	Good	3.9	255.4	2	1	21	6	19	1.4	99.8	metab	(30) (68)
Atropine	532	17.49	---	205	0.99	1.4	31	1.2	61	0.85	Good	1.3	289.4	4	1	50	5	21	-1.2	99.7	both	(30) (69)
Azelastine	630	19.14	600	---	0.99	3	31	3.3	96	0.95	Good	4	381.9	3	0	36	3	27	2.1	98	metab	(30) (70)
Azithromycin	700	11.22	72	---	0.01	3.7	4.3	4.6	89	4.3	Bad	2.6	749	14	5	180	7	52	0.7	99.1	metab	(30) (71)
Aztreonam	105	4.95	112.8	---	0.12	0.17	3.1	3.9	79	2.2	Bad	0.3	435.4	11	4	202	7	28	-4.5	100	excr	(30) (72)
Betamipron	644	5.61	96	39.5	0.98	0.34	14	0.68	40	0.59	Good	0.7	193.2	3	2	66	4	14	-2.4	99.9	excr	(30) (73)
Betaxolol	238	50.82	240	---	0.68	1.7	19	2.8	79	1.2	Moderate	2.3	307.4	4	2	51	11	22	0.3	99.1	metab	(30) (74)
Biapenem	175	4.29	56.4	27.5	0.02	0.7	6.3	1.7	44	1.9	Bad	-6.3	351.4	6	2	100	4	24	-5.7	100	excr	(30) (75)
Biperiden	840	22.44	324	---	1	3.5	28	0.97	95	0.95	Good	4.9	311.5	2	1	23	5	23	2.8	99.3	metab	(30) (76)
Bisoprolol	259	4.29	94.8	60	0.64	1.6	20	2.8	74	1.5	Moderate	1.8	325.4	5	2	60	12	23	-0.2	99.1	both	(30) (77)
brl-42715	840	45.62	252	110	0.38	0.023	9.7	0.81	30	0.77	Good	-0.7	266.3	6	1	88	2	18	-4.4	100	excr	(31) (251)
Brotizolam	140	7.59	132	65	1	3.8	24	0.61	99.5	0.49	Good	2.7	393.7	3	0	43	1	22	2.7	0	metab	(30) (78)
Bupivacaine	301	25.08	384	50	0.9	2.2	35	1.4	92	0.92	Good	3.7	288.4	2	1	32	5	21	3.1	90	metab	(30) (79)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	Elog D	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	Clog P	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	Clog D	%IONI (0-100%)	ELIM	Ref
Busulphan	168	1.65	231	---	1	1.5	15	0.66	49	0.77	Good	-0.2	262.4	6	0	78	7	14	-0.2	0	metab	(30) (80)
Butorphanol	2870	30.096	696	---	0.99	2.6	20	1.2	95	1.1	Good	3.7	327.5	3	2	44	2	24	3	79	metab	(30) (81)
Caffeine	98	4.125	---	15.3	1	-0.1	38	0.57	30	0.57	Good	0	194.2	3	0	58	0	14	0	0	metab	(30) (82)
Candoxatrilat	161	4.95	69.6	---	0.56	0.83	4.5	2.1	62	1	Moderate	0.6	399.5	7	3	122	11	28	-4.1	100	excr	(30) (83)
Captopril	840	4.29	120.96	94.6	0.83	-0.28	11	0.62	32	0.71	Good	0.9	217.3	4	2	58	3	14	-2.6	100	metab	(30) (84)
Carboplatin	105	3.795	39.6	364.5	0.83	-0.28	11	0.62	32	0.71	Good	0.9	217.3	4	2	58	3	14	-2.6	100	excr	(30) (85)
Carmustine (BCNU)	5460	---	213.6	105	1	-0.16	29	0.58	71	0.58	Good	1.3	214.1	3	1	62	5	12	1.3	0	excr	(30) (86)
Carumonam	105	7.26	66	22.5	0.07	0.39	2.8	4.8	74	4.4	Bad	-1.2	466.4	13	5	254	10	30	-6.1	100	excr	(30) (87)
Caspofungin	9.8	0.1419	---	1.5	0.06	2.5	3.2	13	78	13	Bad	-2.9	1093.3	18	16	412	23	77	-6.7	100	metab	(30) (88)
Cefazolin	62.3	1.782	42	9.5	0.01	0.22	3.2	6.4	79	3.4	Bad	-1.2	454.5	11	2	156	7	29	-4.9	100	excr	(30) (89)
cefclidin	105	2.93	43.2	17	0.02	0.73	2.6	9.3	76	7.2	Bad	-4.5	551.6	11	4	203	8	37	-4	100	excr	(31) (252)
Cefepime	154	3.63	26.4	8	0	0.77	2.7	6.6	65	5.4	Bad	-3.1	481.6	9	3	147	7	32	-2.5	100	excr	(30) (90)
Cefixime	70	1.98	4.8	---	0	-0.13	2.8	4.2	74	2.8	Bad	0.3	453.5	11	4	185	8	30	-4.5	100	excr	(30) (91)
Cefmenoxime	255.5	2.4618	106.92	---	0	0.45	2.8	8.6	87	3.9	Bad	0.3	511.6	13	3	191	8	33	-3.5	100	excr	(30) (92)
Cefmetazole	105	8.349	96	16.5	0.03	0.36	3.5	5.2	83	2.1	Bad	-1.3	471.5	12	2	163	9	30	-5.1	100	excr	(30) (93)
Cefodizime	42.7	0.363	49.2	6	0	0.7	2.8	8.7	91	4.2	Bad	1.1	584.7	13	4	197	10	37	-3.7	100	excr	(30) (94)
Cefoperazone	91	7.59	69.6	4.8	0	0.86	2.6	11	83	8.2	Bad	-0.2	645.7	13	4	220	9	44	-3.9	100	excr	(30) (95)
Ceforanide	46.2	1.782	78	---	0	0.34	2	11	82	5.9	Bad	-3.4	519.6	12	4	194	10	35	-6.9	100	excr	(30) (96)
Cefoselis	123.9	3.168	42	9.5	0.02	0.73	2.3	9.3	70	4.8	Bad	-0.3	522.6	12	5	198	9	35	-2.8	100	excr	(30) (97)
Cefotetan	29.4	4.2174	48	8.5	0.05	0.73	3.4	8.4	88	4.8	Bad	-1.5	575.6	15	4	220	9	36	-6.3	100	excr	(30) (98)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Cefozopran	147	3.102	36	9.5	0	0.48	2.8	12	79	5.5	Bad	-3.7	516.5	11	3	181	7	35	-3.2	100	excr	(30) (99)
Cefpimizole	119	---	7.2	15	0.04	1.1	2.7	14	83	11	Bad	-6.9	671.7	12	6	240	12	46	-7.3	100	excr	(30) (93)
Cefpiramide	33.6	3.135	68.4	2.5	0.01	0.86	2.4	7.7	91	8.5	Bad	1.9	612.6	13	5	213	9	42	-1.6	100	excr	(30) (100)
Cefpirome	133	3.135	38.4	12	0.01	0.66	2.3	9.4	84	6.1	Bad	-2.6	515.6	9	3	151	7	35	-2.1	100	excr	(30) (101)
Ceftazidime	168	2.871	38.4	10.5	0	0.68	2.6	9.4	88	5.5	Bad	-3.8	547.6	11	4	188	9	37	-4.2	100	excr	(30) (102)
Ceftizoxime	147	6.3789	39	29.65	0.01	0.25	2.4	2.7	68	1.8	Moderate	0.3	383.4	9	3	147	5	25	-3.4	100	excr	(30) (103)
Ceftriaxone	18.2	6.6	47.4	0.95	0	0.3	3.1	11	85	8.5	Bad	0	554.6	14	4	209	8	36	-3.9	100	excr	(30) (104)
Cicaprost	266	16.17	---	71.5	0.63	1.8	10	1.9	94	0.97	Good	2.2	374.5	5	3	87	10	27	-1.3	100	excr	(30) (105)
Cidofovir	175	0.231	---	17.5	0.81	-0.28	3	0.91	19	1.1	Bad	-2.4	279.2	8	4	155	6	18	-6.3	---	excr	(30) (106)
Ciprofloxacin	581	8.91	216	23.5	0.13	-0.41	3.8	3.3	54	2.6	Good	-0.2	331.3	6	2	73	3	24	-2.2	100	excr	(30) (107)
Citalopram	301	27.06	168	200	0.99	3.3	36	1	93	0.66	Good	3.1	324.4	3	0	36	5	24	1	99.3	metab	(30) (108)
Clazosentan	735	3.861	34.68	95	0.4	1.9	4.5	7.1	99	4.1	Bad	2.4	577.6	13	3	200	11	41	-0.6	100	excr	(30) (109)
Clevidipine	9940	106.92	1956	---	0.42	2.7	28	4.6	98	2.3	Moderate	5.5	456.3	7	1	91	10	30	5.5	0	metab	(30) (110)
Clindamycin	315	13.2	73.2	---	0.05	2	6.2	2.6	60	1.6	Moderate	2.6	425	7	4	102	7	27	1.5	96	metab	(30) (111)
Clonazepam	61.6	23.265	288	71.5	0.99	1.9	34	1.6	97	0.79	Good	2.4	315.7	4	1	87	2	22	2.4	0	metab	(30) (112)
Cocaine	2240	83.49	584.4	---	0.95	1.6	31	1	75	0.78	Good	2.6	303.4	5	0	56	5	22	1	97	metab	(30) (113)
coumarin	1190	6.66	264	170	0.99	1.5	36	0.53	84	0.51	Good	1.4	146.1	2	0	26	0	11	1.4	0	metab	(31) (253)
cyclophosphamide	182	4	240	100	1	1.3	27	0.53	65	0.59	Good	0.8	261.1	2	1	51	5	14	0.8	0	metab	(31) (254)
Cyclosporine	525	0.561	97.2	---	0.02	3.7	3	13	96	7.7	Bad	14.4	1202.6	12	5	279	15	85	14.4	0	metab	(30) (114)
Darifenacin	840	19.47	468	---	0.98	4.4	26	2.4	97	1.2	Good	3.6	426.6	3	1	56	7	32	1.8	99	metab	(30) (115)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	Elog D	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	Clog P	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	Clog D	%IONI (0-100%)	ELIM	Ref
Decitabine	9100	2.607	103.2	---	0.91	-0.19	3.4	0.64	24	0.67	Bad	-1.9	228.2	7	3	121	2	16	-1.9	0	metab	(30) (116)
Dexamethasone	231	1.056	76.8	---	1	2	18	2.1	89	2.9	Good	1.8	392.5	5	3	95	2	28	1.8	0	metab	(30) (117)
Dexloxiglumide	259	1.9833	368.4	---	0.67	1.2	15	3.9	97	1.3	Bad	4.3	461.4	5	2	96	14	30	1.5	99.9	metab	(30) (118)
Diclofenac	245	5.544	16.8	42.5	0.94	1.3	23	0.81	99	0.67	Good	4.7	296.2	3	2	49	4	19	1.6	99.9	metab	(30) (119)
Didanosine	770	49.665	303.6	136	0.95	-0.037	19	0.76	26	0.68	Good	-0.3	236.2	6	2	93	2	17	-2.8	100	both	(30) (120)
Diflomotecan	589.4	7.59	258	---	0.73	2.5	32	5.1	95	2.5	Good	0.9	412.4	5	1	80	1	30	0.9	0	metab	(30) (121)
disopyramide	168	11.32	348	95	0.91	1.2	32	1.3	87	0.98	Good	2.6	339.5	3	1	59	8	25	0.1	99.8	both	(31) (255)
Dofetilide	364	21.945	122.4	---	0.81	1.7	14	4.6	75	2.6	Moderate	2	441.6	6	2	105	11	29	1.1	88	both	(30) (122)
Dolasetron	12600	23.76	324	385	0.94	1.5	27	2.6	85	1.3	Good	2.3	324.4	4	1	62	3	24	2.3	6	metab	(30) (123)
dopa (l)	1610	36.3	228	85	0.83	-0.15	3.6	0.8	20	1.2	Bad	-2.8	197.2	5	4	104	3	14	-5.3	100	metab	(31) (256)
Doripenem	228.2	11.781	56.4	38.5	0.11	0.75	2.7	4.8	66	3.3	Bad	-3.8	420.5	8	5	162	7	27	-6.3	100	excr	(30) (124)
Doxazosin	112	9.9	156	---	0.88	2.1	29	5.4	95	2.4	Moderate	4	451.5	9	1	112	4	33	4	10	metab	(30) (125)
doxorubicin	1190	11.32	204	140	0	1.9	3.3	7.5	57	6.3	Bad	0.3	543.5	12	6	206	5	39	-1.4	100	both	(31) (257)
Enprofylline	280	3.96	28.8	---	0.93	-0.97	14	0.68	18	0.57	Good	0.7	166.2	3	2	61	1	12	0.7	0	excr	(30) (126)
Eptaloprost	4634	56.1	---	315.5	0.64	1.9	9.4	2	96	1.2	Moderate	2.6	402.5	5	3	87	12	29	-0.1	99.8	metab	(30) (127)
Eritoran	0.91	0.0825	0.228	---	0.26	3.5	6.5	5.9	99.1	8	Bad	19.1	1311.7	18	7	304	59	89	13.7	100	metab	(30) (128)
Ertapenem	31.5	3.3	---	2.35	0.11	0.62	1.7	9.4	65	4.5	Bad	-1.8	475.5	9	5	156	7	33	-5.9	100	excr	(30) (129)
Erythromycin	392	24.09	228	158	0	3.6	4	5.5	88	4.8	Bad	1.6	733.9	14	5	194	7	51	0.9	85	metab	(30) (130)
Ethinylestradiol	490	18.15	---	180	0.58	3.3	29	0.97	99	0.69	Good	3.9	296.4	2	2	40	0	22	3.9	0	metab	(30) (131)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
ethosuximide	10.5	1.03	5.04	1.65	1	-0.32	28	0.61	28	0.59	Good	0.4	141.2	2	1	46	1	10	0.4	0	metab	(31) (196)
Etomidate	910	30.69	204	---	1	2.3	46	0.52	94	0.48	Good	2.4	244.3	3	0	44	5	18	2.4	0	excr	(30) (132)
Etoposide	35	7.59	156	7.5	0.04	2.6	8.7	7.1	87	3.5	Bad	0	588.6	13	3	161	5	42	0	0	both	(30) (133)
Famotidine	462	7.26	103.2	75	0.89	0.79	6.3	2	54	1.6	Bad	-0.6	337.5	9	4	176	7	20	-1.2	77	excr	(30) (134)
Felodipine	770	20.13	396	---	0.23	3.4	34	2.2	98	1.5	Moderate	5.3	384.3	5	1	65	6	25	5.3	0	metab	(30) (135)
Fentanyl	329	19.14	648	---	1	3.5	34	1	95	0.88	Good	3.6	336.5	2	0	24	6	25	2.5	96	metab	(30) (136)
Flecainide	343	11.22	288	---	0.91	1.8	31	13	45	3.1	Good	3.7	414.3	4	2	60	9	28	1.5	99.5	metab	(30) (137)
Fleroxacin	168	1.914	19.2	20	0.11	0.35	13	3.5	42	1.5	Good	0.2	369.3	6	1	64	4	26	-2	---	excr	(30) (138)
flomoxef	420	6.33	60	40	0.06	0.82	3.3	6	82	2.2	Bad	-1.2	496.5	12	3	169	11	32	-4.8	100	excr	(31) (258)
Fluconazole	21.7	1.386	7.8	---	1	1.4	26	0.8	83	0.68	Good	-0.4	306.3	5	1	82	5	22	-0.4	0	excr	(30) (139)
Flumazenil	1120	48.51	192	---	0.99	1.5	45	0.8	84	0.61	Good	1.3	303.3	4	0	64	3	22	1.3	0	metab	(30) (140)
flunisolide	840	2.93	154.8	95	1	1.9	36	4.5	96	1.3	Good	2.4	434.5	6	2	93	2	31	2.4	0	metab	(31) (259)
Flunitrazepam	98	26.4	936	---	0.98	2.3	36	1.2	96	0.7	Good	1.8	313.3	4	0	78	2	23	1.8	0	metab	(30) (141)
fluvastatin	1120	10.66	60	175	0.87	2.1	9.7	2.6	98	1.5	Good	4	411.5	4	3	83	8	30	0.9	99.9	metab	(31) (260)
Furosemide	112	2.31	235.2	17	0.84	0.33	5	1.7	90	0.94	Good	1.9	330.7	5	3	123	5	21	-1.2	100	excr	(30) (142)
Gabapentin	119	3.003	---	11.5	0.51	1.7	4.9	2.3	73	1.3	Moderate	1	382.4	6	4	115	13	26	-1.7	99.8	excr	(30) (143)
Galanthamine	392	10.461	147.6	---	0.97	1.5	36	0.78	72	0.8	Good	1	287.4	4	1	42	1	21	0.4	77	metab	(30) (143)
Garenoxacin	86.1	3.993	29.16	16.95	0.46	1.4	4.3	4.9	94	2.3	Good	0.7	426.4	6	2	79	5	31	-1.5	100	excr	(30) (144)
Gatifloxacin	196	6.369	50.4	51	0.11	-0.23	3.2	4.2	55	2.9	Good	0.2	375.4	7	2	82	4	27	-2.1	100	excr	(30) (145)
Gavestinel	6.23	0.396	25.2	22	0.67	1.2	15	1.4	99	0.86	Moderate	5.2	375.2	3	3	82	4	25	2.1	100	metab	(30) (146)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Gemcitabine	2240	1.65	129.12	885	0.92	1.3	5.4	0.68	23	0.6	Good	-0.7	263.2	6	3	108	2	18	-0.7	0	metab	(30)(147)
Gentamicin	70	2.574	25.2	---	0	1.8	2.6	2.7	33	2.5	Bad	-2.4	449.5	12	8	214	6	31	-8.1	100	excr	(30)(148)
Haloperidol	546	28.446	---	39	1	2.8	33	2.9	96	1.2	Good	3.8	375.9	3	1	41	6	26	2.7	92	metab	(30)(149)
hi-6	224	3.26	44.4	43	0.89	0.6	21	1.8	61	0.96	Bad	-7.2	288.3	4	2	93	6	21	-7	100	excr	(31)(261)
Hydroxystaurosporine, 7-	0.259	21.45	122.4	---	0.54	2.9	16	7	96	4.1	Good	3.4	482.5	5	3	90	2	36	2.1	95	metab	(30)(150)
Ibuprofen	57.4	1.584	5.88	---	0.97	0.47	19	0.63	97	0.66	Good	3.7	206.3	2	1	37	4	15	0.8	99.9	metab	(30)(151)
Ifetroban	448	28.875	---	95.5	0.68	1.4	12	4.4	92	1.3	Moderate	3.4	440.5	5	2	102	11	32	0.7	99.8	metab	(30)(152)
Iloprost	1120	10.692	806.4	---	0.66	1.9	9.1	1.3	95	0.94	Good	2.7	360.5	4	3	78	9	26	0.1	99.8	metab	(30)(153)
Imatinib	231	6.567	468	60	0.68	1.9	14	5.9	97	5	Good	4.5	493.6	7	2	86	7	37	3.9	70	metab	(30)(154)
Imipenem	210	4.785	51.6	28.5	0.1	1.9	3.8	3	19	2.9	Bad	-1.4	299.4	6	4	114	7	20	-3.9	100	metab	(30)(155)
Indinavir	1260	29.37	180	178.5	0.11	2.5	3	12	62	8.6	Bad	3.7	613.8	7	4	118	12	45	3.6	14	metab	(30)(156)
indomethacin	140	0.14	0.024	65	0.85	1.5	25	1.2	98	0.76	Good	4.1	356.8	4	1	64	5	25	1.1	99.9	both	(31)(262)
Inogatran	427	27.39	108	130	0	1.5	2.9	7.1	94	5.7	Bad	1.9	653.4	11	5	186	5	39	0.4	---	excr	(30)(157)
Iododoxorubicin	9800	12.078	78	216.5	0.43	0.08	2.5	6	56	5.3	Bad	-0.1	438.6	6	6	161	12	31	-3.4	100	metab	(30)(158)
Iomeprol	98	2.442	40.8	---	0.4	1.1	2.8	6.2	73	2.3	Bad	-2.3	777.1	8	7	180	10	31	-2.3	0	excr	(30)(159)
Ipratropium	2198	29.7	499.2	---	0.68	2.1	34	1.5	93	1.1	Bad	-2.2	332.5	3	1	47	6	24	-2.2	100	both	(30)(160)
Irinotecan	490	18.381	46.8	66.5	0.53	2.8	18	9.8	94	7.4	Moderate	2.7	586.7	8	1	113	5	43	1.1	99	metab	(30)(161)
Isosorbide Dinitrate	2170	40.26	---	294	0.89	1.7	11	0.66	60	0.65	Bad	-3.5	236.1	8	0	129	4	16	-3.5	0	metab	(30)(162)
Ketamine	1330	37.851	386.4	---	0.97	1.8	46	0.49	69	0.51	Good	2.9	237.7	2	1	29	2	16	2.9	10	metab	(30)(163)
Ketanserin	469	1.254	296.4	---	0.98	2	30	3.9	93	2	Good	3	395.4	4	1	70	5	29	2.6	60	metab	(30)(164)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
ketorolac	24.5	1.2	15.6	3	0.8	0.21	17	0.71	88	0.64	Good	1.6	255.3	3	1	59	3	19	-1.4	99.9	both	(31) (263)
L-692429	213.5	0.891	231.6	28.5	0.46	1.9	2.1	10	98	8.4	Moderate	4.1	567.7	7	4	136	10	42	1.6	100	metab	(30) (165)
Lamifiban	133	3.135	84	13	0.5	1	2.9	7.5	69	4.9	Bad	-0.6	468.5	7	5	166	9	34	-3.1	100	excr	(30) (166)
lamivudine	1400	23.98	264	65	0.81	0.36	14	0.6	24	0.56	Bad	-1.5	229.3	6	2	88	2	15	-1.5	0	excr	(31) (264)
latamoxef	84	3.13	26.4	10	0.06	0.49	2.6	7.3	81	4	Bad	-0.8	520.5	13	4	206	9	36	-5.6	100	excr	(31) (265)
Lidocaine	1120	15.411	---	330	0.42	2.3	35	0.94	78	0.74	Good	2	234.3	2	1	32	5	17	1.2	93	metab	(30) (167)
Lubeluzole	119	8.25	499.2	---	0.91	2.5	32	4.1	95	1.6	Good	4.3	433.5	5	1	49	7	30	4.1	41	metab	(30) (168)
Maraviroc	658	24.42	252	---	0.67	3.6	26	7	99.1	5.3	Moderate	3.3	513.7	4	1	63	8	37	0.7	99.9	metab	(30) (169)
Maxipost	1050	14.19	42	---	0.99	4	35	0.6	99.2	0.5	Good	4.1	359.7	2	0	30	3	24	4.1	0	metab	(30) (170)
Melagatran	133	5.577	84	---	0.39	1.1	2	6.5	46	5.7	Bad	-0.8	429.5	6	5	149	9	31	-3.7	100	excr	(30) (171)
Meloxicam	8.4	0.0825	2.04	---	0.49	1.2	24	1.2	85	0.81	Good	2.3	351.4	5	2	100	2	23	-0.6	99.9	metab	(30) (172)
MEN-10755	175	3.564	219.6	---	0.02	2	2.5	9.3	65	9.2	Bad	0.1	642.7	14	7	241	6	46	-2.3	100	metab	(30) (173)
meperidine	1190	84.25	516	5	1	2	41	0.7	82	0.58	Good	2.2	247.3	3	0	30	4	18	1.2	92	metab	(31) (266)
Meropenem	273	8.712	48	37.5	0.04	0.75	3.1	3.7	52	3	Bad	-3.3	383.5	7	3	110	5	26	-6	100	excr	(30) (174)
methotrexate	175	4	14.4	40	0.2	0.19	2	7	74	3.2	Bad	-0.5	454.4	12	5	211	9	33	-5.2	100	metab	(31) (267)
Metoclopramide	399	15.84	277.2	---	0.99	1.4	25	2	56	1.2	Good	2.2	299.8	4	2	68	7	20	0	99.4	both	(30) (175)
Metoprolol	910	28.776	393.6	109.5	0.7	1	23	2	74	1.1	Good	1.5	267.4	4	2	51	9	19	-0.6	99.1	metab	(30) (176)
Metronidazole	59.5	1.914	30	---	0.99	0.31	21	0.6	45	0.62	Good	-0.5	171.2	4	1	84	3	12	-0.5	0	both	(30) (175)
Micafungin	11.9	0.33	9.36	---	0.08	2.5	5.2	8.8	88	9.4	Bad	-2.6	1270.3	23	16	510	18	89	-6.1	100	metab	(30) (177)
Midazolam	371	29.7	422.4	111.5	1	3.6	42	0.58	99	0.48	Good	3.4	325.8	2	0	30	1	23	3.4	1	metab	(30) (178)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Mivacurium (cis/cis)	364	3.267	41.64	---	0.43	4.9	5.1	8.9	99	5.6	Bad	2.6	1029.3	14	0	145	30	74	2.6	100	metab	(30) (179)
mk-571	64.4	12.32	48	9.5	0.54	2.1	21	3.7	99.8	1.5	Moderate	5.7	515.1	6	1	71	11	34	2.6	99.9	metab	(31) (268)
Morphine	1820	19.107	733.2	227	0.99	1.3	14	0.84	34	0.84	Good	0.6	285.3	4	2	53	0	21	-0.3	88	metab	(30) (180)
Moxalactam	50.4	3.003	26.4	11.5	0.06	0.49	2.6	7.3	81	4	Bad	-0.8	520.5	13	4	206	9	36	-5.6	100	excr	(30) (181)
moxestrol	23.8	17.32	62.4	16	0.72	3.3	32	1	98	0.71	Good	2.6	326.4	3	2	50	1	24	2.6	0	metab	(31) (269)
Moxifloxacin	168	14.025	44.4	57.5	0.18	0.51	3.3	4.9	67	4.2	Good	0.5	401.4	7	2	82	4	29	-2.1	100	metab	(30) (182)
naltrexone	3360	26.64	1080	330	1	1.6	15	2.3	45	1.8	Good	0.4	341.4	5	2	70	2	25	-0.1	56	metab	(31) (270)
naproxen	4.9	0.14	0.48	3.05	0.85	0.49	22	0.61	96	0.62	Good	2.8	230.3	3	1	47	3	17	0.3	99.7	metab	(31) (271)
Napsagatran	448	21.582	313.2	96	0.34	0.94	2.3	11	67	7.3	Bad	1.3	558.7	7	5	186	12	39	-1.2	100	excr	(30) (183)
Nicardipine	770	53.79	444	135	0.15	3.5	16	5	89	4.2	Moderate	5.2	479.5	8	1	114	11	35	5	44	metab	(30) (184)
nicardipine	490	38.3	576	135	0.15	3.5	16	5	89	4.2	Moderate	5.2	479.5	8	1	114	11	35	5	44	metab	(31) (272)
Nimodipine	1050	6.468	216	165	0.19	2.8	23	4	90	2.6	Good	4	418.4	8	1	120	10	30	4	0	metab	(30) (185)
Nisoldipine	1050	15.114	446.4	---	0.23	3.9	25	4.5	90	2.2	Good	4.6	388.4	7	1	110	8	28	4.6	0	metab	(30) (186)
Ofloxacin	175	4.356	278.4	---	0.17	0.13	11	3.1	47	1.8	Good	0	361.4	7	1	73	2	26	-2.2	100	excr	(30) (187)
Oleandomycin	637	16.83	144	---	0.01	3.5	4.5	4.6	93	4.6	Bad	1.6	687.9	13	3	166	6	48	0.8	85	metab	(30) (188)
Oseltamivir acid	336	8.25	63.6	---	0.69	0.35	2.7	1.3	53	1.8	Bad	-1.2	284.4	5	3	102	6	20	-3.7	100	metab	(30) (189)
Paclitaxel	448	3.531	---	31	0.07	3.6	7.5	7.6	97	8.5	Bad	4.7	853.9	14	4	221	14	62	4.7	0	metab	(30) (190)
Panipenem	182	9.141	58.2	32.6	0.03	0.99	4.7	2.4	40	2.1	Bad	-1.8	339.4	6	3	105	5	23	-4.3	100	excr	(30) (191)
Pefloxacin	140	9.3951	94.68	55.15	0.19	-0.085	14	1.9	49	1.4	Good	0.2	333.4	6	1	64	3	24	-2	---	both	(30) (191)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
pelrinone	280	9.32	132	65	0.91	0.46	31	0.9	55	0.71	Good	-0.7	241.3	6	2	90	3	18	-0.9	41	excr	(31) (273)
Pentamidine	5180	36.795	727.2	---	0.95	2.6	7.9	2	85	1.2	Moderate	2.3	340.4	4	4	118	10	25	-0.7	100	metab	(30) (192)
Pentobarbital	32.9	2.772	15.6	---	1	0.77	30	0.96	73	0.84	Good	2.1	226.3	3	2	75	4	16	1.9	33	metab	(30) (193)
Pentoxifylline	2730	2.4024	444	---	0.97	0.6	42	1	64	0.93	Good	0.1	278.3	4	0	76	5	20	0.1	0	metab	(30) (194)
Phencyclidine	357	21.879	649.2	183	1	3.3	34	0.6	97	0.59	Moderate	5.1	243.4	1	0	3	2	18	4.2	87	metab	(30) (195)
Phenobarbital	4.41	0.264	1.2	---	1	1.4	25	0.88	50	0.73	Good	1.4	232.2	3	2	75	2	17	1	55	metab	(30) (196)
phenytoin	39.9	2.46	33.6	39.5	0.99	2.1	31	1.1	94	0.61	Good	2.1	252.3	2	2	58	2	19	2.1	11	metab	(31) (274)
Pindolol	539	15.939	1070.4	---	0.54	0.57	23	1.1	45	1.1	Good	1.7	248.3	3	3	57	6	18	-0.4	99.2	both	(30) (197)
Piperacillin	280	5.841	79.2	36	0	1.3	2.4	8.8	63	8.1	Moderate	1.7	517.6	8	3	156	6	36	-2	100	excr	(30) (198)
Pirmenol	126	20.46	99.6	24.6	0.92	3	27	1	96	0.96	Good	3.4	338.5	3	1	36	6	25	0.9	99.8	both	(30) (199)
Prazosin	329	22.704	169.2	---	0.94	1.9	39	4	91	1.6	Good	2.5	383.4	7	1	107	4	28	2.5	10	metab	(30) (200)
Prednisone	175	51.051	298.8	49	1	1.6	23	2.3	86	1.9	Good	1.7	358.4	5	2	92	2	26	1.7	0	metab	(30) (201)
Procainamide	700	39.6	104.4	---	0.99	0.45	16	1.6	15	1.1	Good	1.4	235.3	3	2	58	6	17	-0.9	99.7	excr	(30) (202)
Propafenone	1120	9.273	334.8	---	0.31	2	32	4.6	85	1.9	Moderate	3.6	341.4	4	2	59	11	25	2.2	94	metab	(30) (203)
Propofol	2520	35.409	477.6	---	0.97	2.7	37	0.51	96	0.5	Good	3.9	178.3	1	1	20	2	13	3.9	0	metab	(30) (204)
Propranolol	840	31.119	621.6	104	0.39	1.6	35	1.1	85	1	Good	2.8	259.3	3	2	41	6	19	0.7	99.1	metab	(30) (205)
Quinidine	280	6.1479	42.96	112	0.59	1.4	35	0.97	87	0.99	Good	2.8	324.4	4	1	46	4	24	0.9	99	metab	(30) (206)
Quinine	133	29.014	97.32	---	0.59	1.4	35	0.97	87	0.99	Good	2.8	324.4	4	1	46	4	24	0.9	99	metab	(30) (207)
Rabeprazole	280	27.192	1032	---	0.85	1.9	40	2.7	94	1	Good	2.1	359.4	5	1	77	8	25	2.1	3	metab	(30) (208)
Ranitidine	672	10.527	139.2	---	0.8	1.6	16	2.1	56	1.6	Good	0.7	314.4	6	2	86	10	21	-0.4	91	excr	(30) (209)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Recainam	315	27.06	156	133.5	0.88	1.1	27	2.3	82	1.9	Good	1.9	263.4	2	3	53	6	19	-0.8	99.9	excr	(30) (210)
Remikiren	812	39.27	296.4	100	0.22	3	1.5	10	92	6.3	Bad	3.6	630.8	7	5	161	16	44	3.4	17	metab	(30) (211)
Remoxipride	119	56.1	58.8	---	0.99	1.4	36	1.3	79	1	Good	3.3	371.3	4	1	51	6	22	1.4	97	metab	(30) (212)
Ribavirin	364	14.19	---	18.5	0.8	-0.6	2.2	0.78	19	0.76	Bad	-2.8	244.2	7	4	144	3	17	-2.8	0	metab	(30) (213)
Ritipenem	528.5	5.115	88.8	23.25	0.46	1.3	6.9	2.4	57	1.6	Moderate	-0.8	360.3	9	2	145	9	24	-0.8	0	metab	(30) (214)
ro 25-6833	26.6	0.32	32.4	3.9	0.06	0.93	3.1	11	89	5.2	Bad	-1.1	546.5	10	4	179	7	36	-5.3	---	both	(31) (275)
Ro25-6833	26.6	0.3135	32.4	3.85	0.06	0.93	3.1	11	90	5.2	Bad	-1.1	546.5	10	4	179	7	36	-5.3	---	both	(30) (215)
Romidepsin	518	206.25	---	139.5	0.39	2.5	7	12	93	3.5	Moderate	3.4	540.7	8	4	143	2	36	3.4	0	metab	(30) (216)
Sch34343	525	7.524	106.8	33.5	0.1	0.58	2.9	2.1	57	1.3	Bad	-1	334.4	8	3	130	7	21	-4.3	100	both	(30) (217)
Sematilide	259	8.448	108	---	0.93	0.6	20	2.3	36	1.6	Good	1.4	313.4	4	2	79	8	21	-0.9	100	excr	(30) (217)
Semaxanib	980	14.85	624	138.5	0.95	1.6	46	0.69	92	0.55	Good	2.8	238.3	1	2	45	1	18	2.8	0	metab	(30) (218)
Sildenafil	637	15.84	144	---	0.76	2.4	33	7.2	91	6.4	Good	2	474.6	7	1	109	7	33	2	4	metab	(30) (219)
Sinitrodil	2071.3	28.017	764.4	131.5	0.98	1.4	37	0.68	63	0.58	Good	-0.8	238.2	5	0	85	4	17	-0.8	0	metab	(30) (220)
Sitagliptin	420	14.85	109.2	---	0.94	2.3	22	2.4	85	2.8	Good	0.7	407.3	4	1	77	5	28	0.6	39	excr	(30) (221)
Sparfosic_Acid	85.4	5.742	49.2	11.5	0.63	0.74	2.3	0.95	27	0.74	Bad	-2.2	255.1	8	5	171	6	16	-8.4	100	metab	(30) (222)
Stavudine	574	6.666	---	47	0.86	0.13	14	0.68	24	0.64	Good	-0.5	224.2	4	2	79	2	16	-0.5	2	excr	(30) (223)
sudoxicam	7	0.06	0.48	0.95	0.53	0.94	19	0.91	88	0.71	Good	1.8	337.4	5	2	100	2	22	-1.1	99.9	metab	(31) (276)
Sulfadiazine	38.5	0.363	---	3.2	0.96	0.13	11	0.88	87	0.74	Good	0.1	250.3	5	2	98	3	17	-1.2	89	excr	(30) (224)
Sulfinpyrazone	23.8	0.1518	10.08	2.25	0.95	3	33	1.4	97	0.9	Good	1.7	404.5	3	0	58	6	29	-0.2	99	excr	(30) (225)
Sulfisoxazole	21	0.2145	16.56	---	0.93	-1.2	13	1.1	83	0.85	Good	0.2	267.3	4	2	98	3	18	-1.2	99.7	excr	(30) (175)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
Sumatriptan	1330	9.24	166.8	---	0.95	0.79	21	2.6	49	1.9	Good	0.7	295.4	3	2	65	6	20	-1.1	99.2	both	(30) (226)
Susalimod	4.9	20.46	240	9.5	0.63	1.4	6.8	2.5	99	1	Good	4.3	408.4	6	3	117	6	29	0.8	100	excr	(30) (209)
Tacrolimus	49	10.428	2784	22	0.02	4	6.9	7.3	98	6	Bad	5.8	804	12	3	178	7	57	5.8	0	metab	(30) (227)
Tamsulosin	43.4	27.126	231.6	---	0.79	2.3	15	5.7	86	3.2	Moderate	2.2	408.5	6	2	100	11	28	0.6	98	metab	(30) (228)
Tebufelone	623	13.646	370.8	74.5	0.95	3.2	25	0.93	99.4	0.63	Moderate	5.8	300.4	2	1	37	6	22	5.8	3	metab	(30) (229)
Teicoplanin A2-1	14	0.1749	1.2	---	0.13	1.7	2.9	6.9	95	7.7	Failed	---	1877.6	34	24	662	19	132	---	100	excr	(30) (230)
Telavancin	14	0.2805	13.2	4.75	0.14	1.9	3.7	9.5	97	8.1	Bad	1.9	1755.6	31	23	608	30	121	-1.1	100	excr	(30) (191)
Tenofovir	217	---	70.8	81	0.74	0.26	4.2	0.88	26	1	Bad	-1.6	287.2	8	3	146	5	19	-5.5	100	excr	(30) (231)
Tezosentan	567	1.419	---	78	0.4	2.1	4.7	6.7	99	3.8	Bad	3.3	605.6	13	3	200	12	43	0.3	100	excr	(30) (232)
Theophylline	60.2	0.7425	21.6	19	0.94	-1.4	18	0.91	42	0.72	Good	0	180.2	3	1	69	0	13	-0.1	5	metab	(30) (233)
tiazofurine	98	2.3	33.6	17.5	0.75	0.038	2.6	0.84	20	0.71	Bad	-1.9	260.3	6	4	126	3	17	-1.9	0	excr	(31) (277)
tiludronate	21	1.1	6	4.15	0.77	0.62	4.3	0.71	60	0.7	Moderate	0.3	318.6	7	4	135	4	17	-5.2	100	excr	(31) (278)
Tolcapone	133	2.904	22.8	---	0.34	1.3	25	1.5	99	0.84	Good	3.2	273.2	5	2	103	3	20	1	99.8	metab	(30) (234)
Tomopenem	133	5.181	47.52	8.5	0.15	0.63	2.1	9.7	62	6	Bad	-3.8	537.6	9	6	192	9	37	-6.8	100	excr	(30) (235)
Topotecan	910	11.352	211.2	480.5	0.46	1.6	19	7.3	76	4.6	Good	-0.3	423.5	7	2	103	3	31	-0.9	63	both	(30) (236)
Torsemide	37.1	1.2342	1.68	---	0.74	0.96	16	1.6	96	0.97	Good	3.4	348.4	5	3	100	5	24	1.4	100	metab	(30) (237)
Tramadol	455	20.955	655.56	---	0.97	1.1	36	0.78	88	0.81	Good	3.1	263.4	3	1	33	4	19	1.1	99.4	metab	(30) (238)
trimethadione	49	1.9	34.8	8	0.66	2.6	25	5	99.6	1.8	Moderate	5.6	441.5	6	2	85	5	31	4.5	92	metab	(31) (279)
Trimethoprim	147	13.2	76.8	---	0.98	1.2	22	9.4	80	2.1	Good	1	290.3	7	2	106	5	21	0.7	41	metad	(30) (239)
Trimetrexate	53.9	23.463	398.4	42.5	0.87	2.1	21	3.2	97	1.5	Good	1.8	369.4	8	3	118	6	27	0.4	94	metab	(30) (240)

Compound Name	human CL (mL/min)	rat CL (mL/min)	dog CL(mL/min)	monkey CL (mL/min)	CNSa (0-1)	ElogD	Papp (10^-6 cm/sec)	PGPr (BA:AB ratio)	PPB (0-100%)	PGPh (BA:AB ratio)	OrlA	ClogP	MW (Da)	HBA	HBD	PSA (Å^2)	RCB	nonH	ClogD	%IONI (0-100%)	ELIM	Ref
troglitazone	245	7.33	79.2	41.5	0.66	2.6	25	5	99.6	1.8	Moderate	5.6	441.5	6	2	85	5	31	4.5	92	metab	(31) (280)
Trospectomycin	119	1.4124	32.28	---	0.18	1.1	3.3	2.1	31	1.9	Bad	-1.3	374.4	9	5	130	5	26	-2.8	97	excr	(30) (241)
Trovafloxacin	98	4.455	109.56	29.65	0.4	0.8	4.4	5.8	91	2.2	Good	0.3	416.4	7	2	100	3	30	-1.8	100	both	(30) (242)
UK-240455	420	3.96	156	---	0.8	0.87	12	2.1	83	1.3	Good	-0.9	368.2	5	3	116	4	22	-1.1	22	excr	(30) (243)
valproate	7.7	1.4	36	20	1	0.53	13	0.52	81	0.55	Good	2.8	144.2	2	1	37	5	10	0.2	99.7	metab	(31) (281)
Valproic Acd	11.2	1.386	36.36	21	1	0.53	13	0.52	81	0.55	Good	2.8	144.2	2	1	37	5	10	0.2	99.7	metab	(30) (244)
Venlafaxine	980	21.285	162	205	1	1.5	37	0.72	86	0.85	Good	3.3	277.4	3	1	33	5	20	1.6	99	metab	(30) (245)
Verapamil	1260	11.055	321.6	114	0.36	3.5	20	1.5	99	1.7	Moderate	4.5	454.6	6	0	64	13	33	2.9	97	metab	(30) (246)
Vildagliptin	693	15.939	260.4	125	0.96	1.8	20	1.4	33	1.2	Good	0.7	303.4	4	2	76	3	22	-0.5	94	metab	(30) (247)
vinblastine	840	8.33	264	35	0.01	3.1	5.8	8.8	88	9.1	Bad	5.2	811	12	3	154	10	59	4.7	76	metab	(31) (282)
vincristine	126	0.67	117.6	24	0.1	3.5	5.9	9.4	98	9	Bad	8.2	822	10	2	148	10	60	8.2	1	excr	(31) (283)
Voriconazole	581	3.003	18	---	0.99	2.1	38	0.73	93	0.6	Good	0.5	349.3	5	1	77	5	25	0.5	0	metab	(30) (248)
Vorinostat	1960	42.735	656.4	---	0.9	0.81	19	1.8	84	1	Good	1	264.3	3	3	78	8	19	1	0	metab	(30) (249)
warfarin	2.8	0.12	3.6	0.65	0.83	2.4	31	0.85	97	0.66	Good	2.9	308.3	4	1	64	4	23	0.1	99.9	metab	(31) (274)
Zalcitabine	392	3.696	---	51.5	0.97	0.34	12	0.63	21	0.59	Bad	-1.2	211.2	5	2	88	2	15	-1.3	0	excr	(30) (250)
zidovudine	1680	15.32	168	75	0.83	0.34	10	1.1	23	1	Moderate	-0.6	269.3	6	4	131	3	19	---	---	metab	(31) (284)

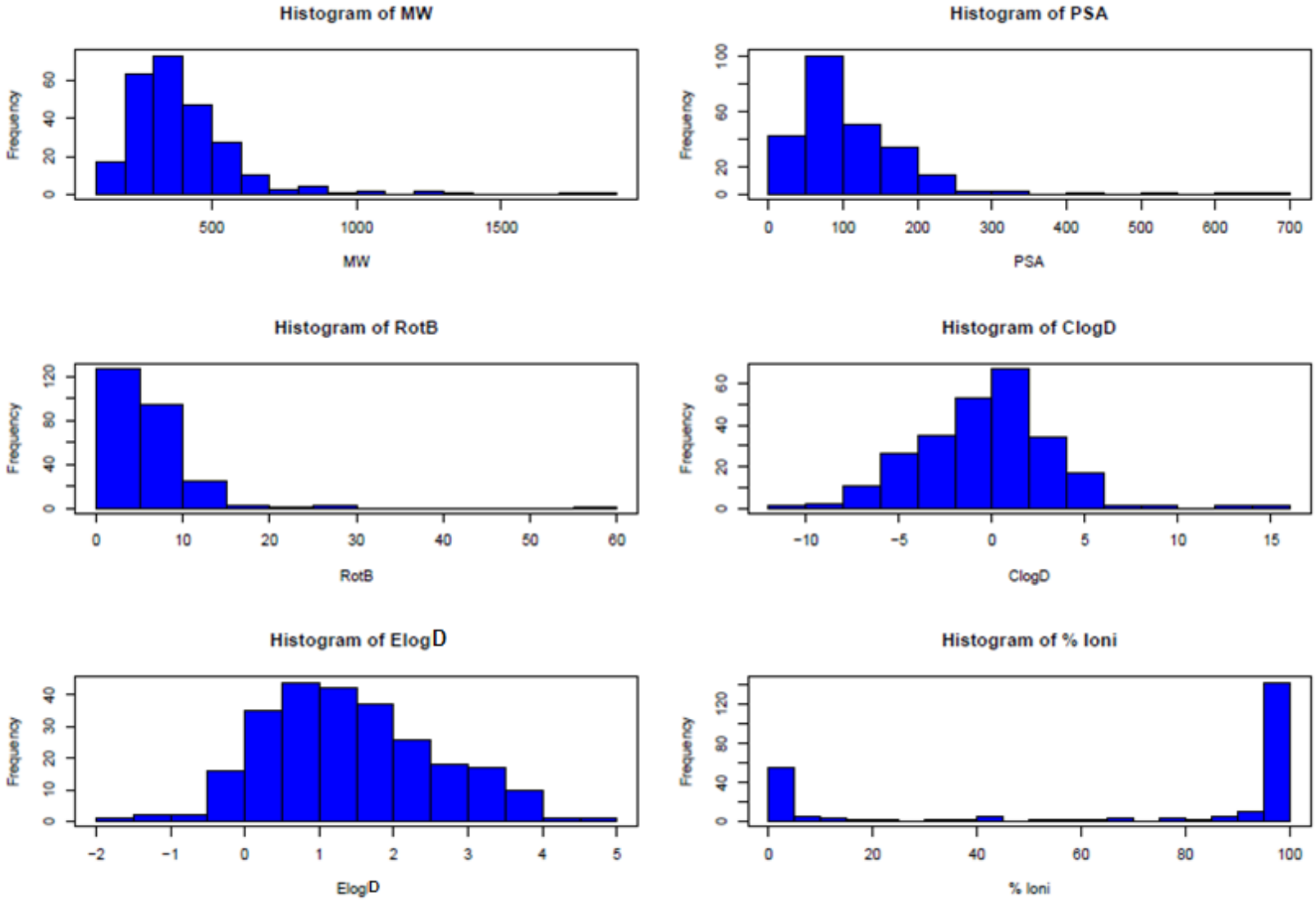
Table 2. AS parameter estimation of basic structure model and final model based on the Nonlinear MEM approach

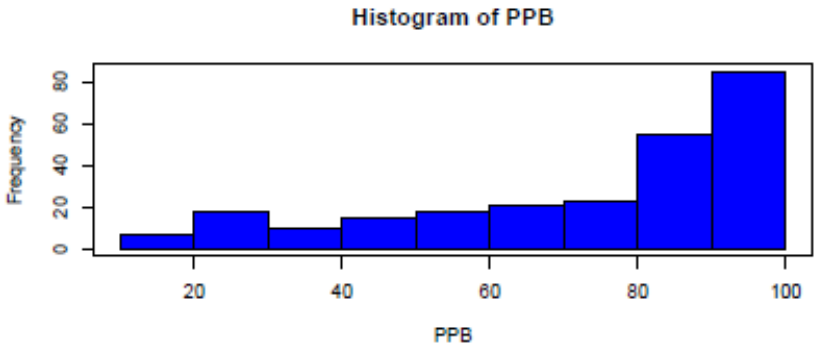
	Basic Structure Model		**Bootstrap**		
				95% CI	
Parameter	**Estimation**	**RSE%**	**Median**	LL	**UL**
AS coefficient	2.06	7.80	2.06	1.73	2.37
AS exponent	0.629	2.93	0.628	0.59	0.66
Inter-drug variability (IDV)					
ŋ AS coefficient	1.04	29.4	1.03	0.56	1.85
η AS exponent	0.413	29.1	0.407	0.10	0.29
Residual error model					
σ_{add}	0.180	---	0.180	---	---
Eta Shrinkage (ŋ - shrinkage)					
AS coefficient	3.43				
AS exponent	2.76				
Epsilon shrinkage (Ɛ-shrinkage)	-251				
	Final Model		**Bootstrap**		
				95% CI	
Parameter	**Estimation**	**RSE%**	**Median**	**LL**	**UL**
AS coefficient	2.08	7.44	2.09	1.8	2.39
AS exponent	0.628	2.94	0.628	0.59	0.66
PSA on AS coefficient	-0.481	-25.2	-0.473	-0.77	-0.24
Inter-drug variability (IDV)					
AS coefficient	0.983	30.5	0.973	0.48	1.65
η AS exponent	0.413	29.2	0.406	0.10	0.30
Residual error model					
σ_{add}	0.180	---	0.180	---	---
Eta Shrinkage (ŋ - shrinkage)					
AS coefficient	3.45				
AS exponent	2.77				
Epsilon shrinkage (Ɛ-shrinkage)	-251				

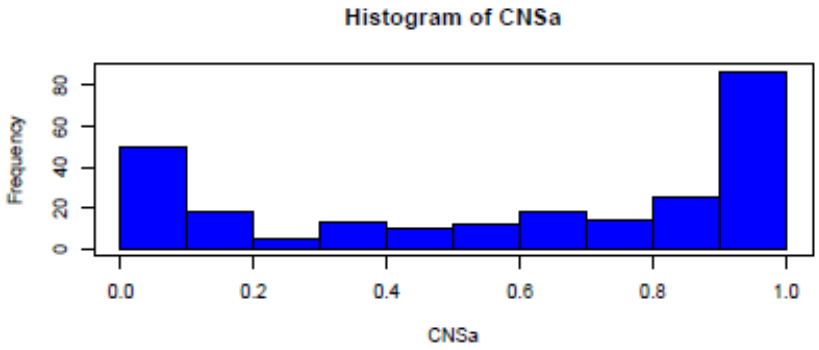
Table 3. Physicochemical and DMPK properties of compounds in the database

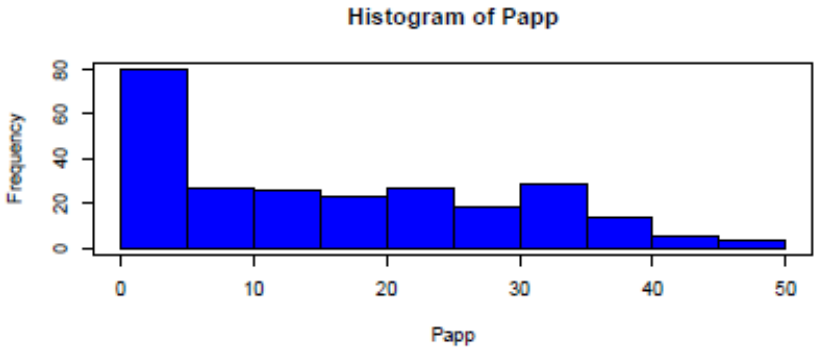
	N	Mean	Median	Range	Q1	Q3
Molecular Weight (MW) (Da)	251	407	360	101 -1878	277	466
Polar Surface Area (PSA) (Å)	251	111	90	3 - 662	60	146
Rotatable Carbon Bound (RCB)	251	6.42	5	0 - 59	3	8
Calculated Logarithm of the Octanol-Water Distribution Coefficient (ClogD)	249	-0.345	-0.1	-11.6 - 14.4	-2.3	1.7
Estimated Logarithm of the Octanol-Water Partition Coefficient (ElogP)	251	1.465	1.4	1.6 - 4.9	0.59	2.1
Percent of Ionization (%Ioni)	243	69.8	99.1	0 - 100	10.5	100
Plasma Protein Binding (PPB)	251	73.8	83	15 - 99.8	57	94
Central Nervous System Absorption (CNSa)	251	0.593	0.7	0 - 1	0.18	0.95
Apparent Permeability through Cell Membrane (Papp)	251	16.5	14	1.5 - 46	3.75	27
Human P-glycoprotein Transporting Property (PGPh)	251	2.47	1.4	0.48 - 13	0.8	3.35
Oral Absorption Property (OrlA)	249					
good	130					
moderate	35					
bad	84					
Elimination Pathway (Elim)	251					
excretion	67					
metabolism	161					
both	24					

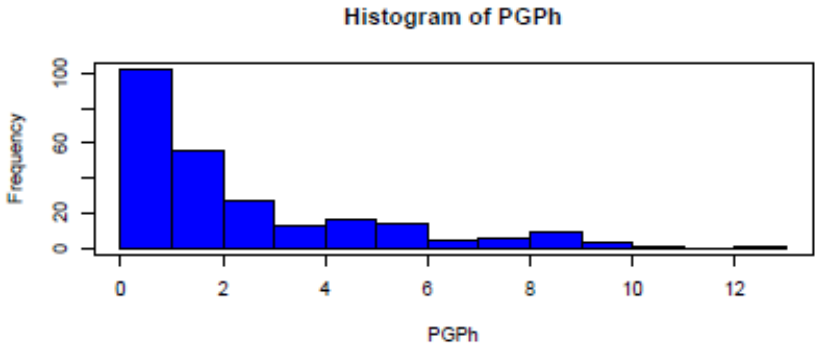
Figure 1. Distribution of the physicochemical and DMPK properties

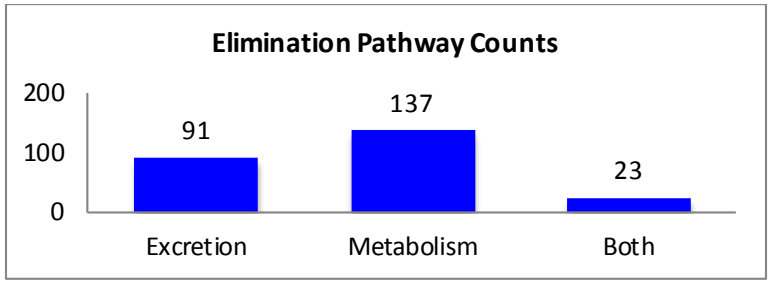



Histogram of PPB
Frequency
0
20
40
60
80
20
40
60
80
100
PPB


Histogram of CNSa
Frequency
0
20
40
60
80
0.0
0.2
0.4
0.6
0.8
1.0
CNSa


Histogram of Papp
Frequency
0
20
40
60
80
0
10
20
30
40
50
Papp


Histogram of PGPh
Frequency
0
20
60
100
0
2
4
6
8
10
12
PGPh


Elimination Pathway Counts
200
100
0
91
137
23
Excretion
Metabolism
Both

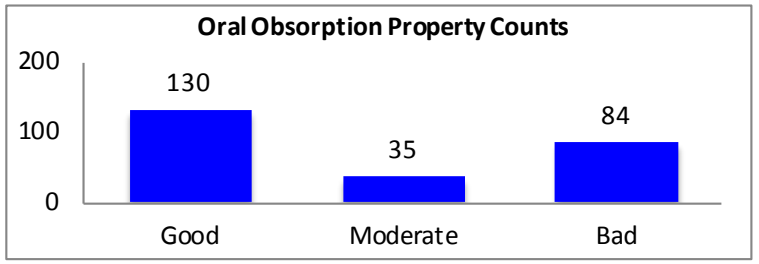

Oral Obsorption Property Counts
200
100
0
130
35
84
Good
Moderate
Bad

Figure 2. Goodness of fit plots of the final AS nonlinear MEM model. (A) and (D). Population Model Predicted versus Observed CLs; (B) and (E). Individual predicted based on final model versus observed CLs; (C). Conditional weighted residuals versus log transformed body weight;

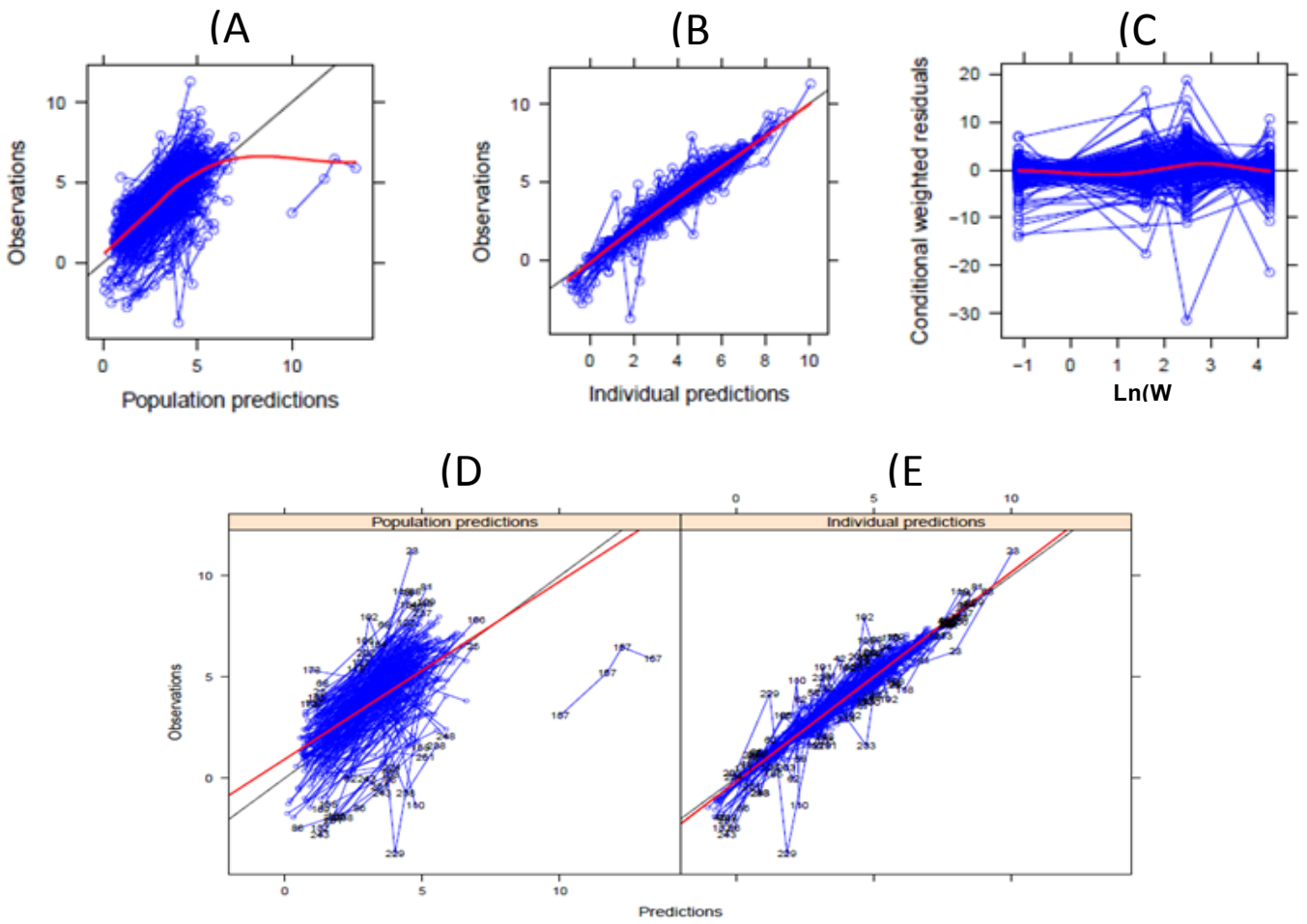
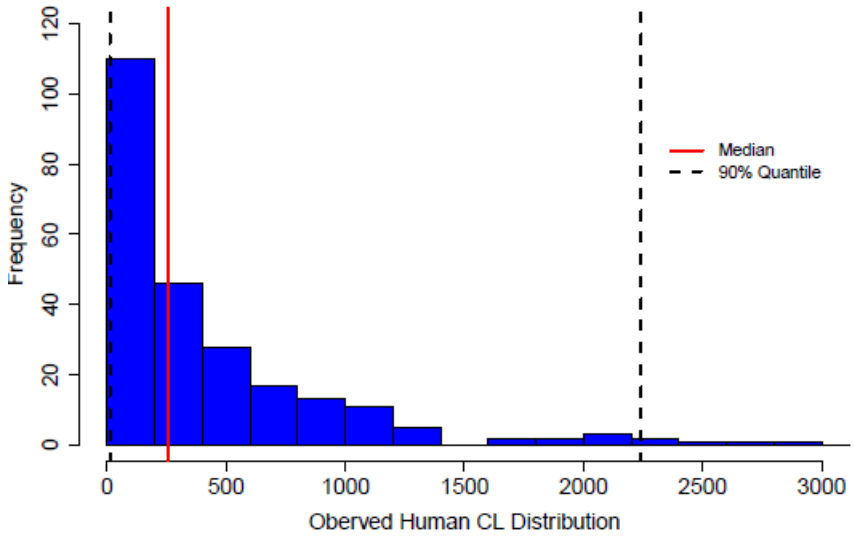


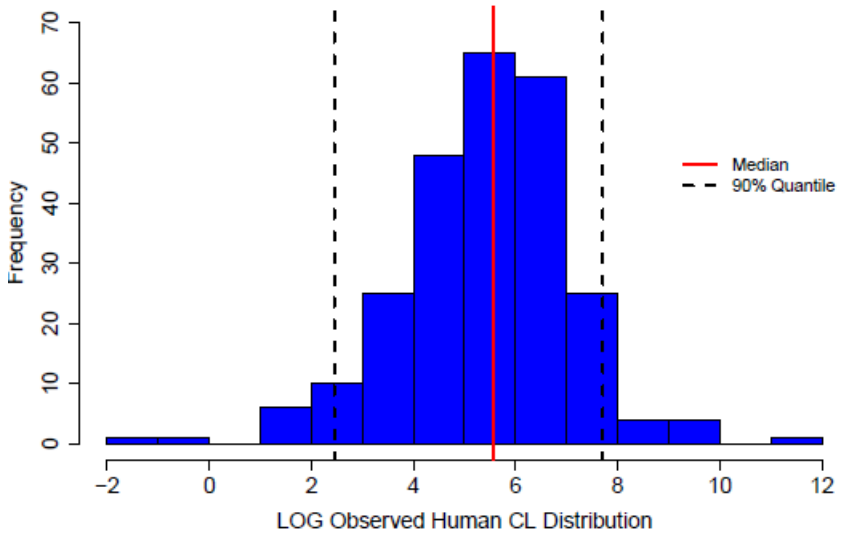
Figure 3. Distribution and central tendency of Observed versus Model Predicted Human CL

1) Observed human CLs distribution

a.

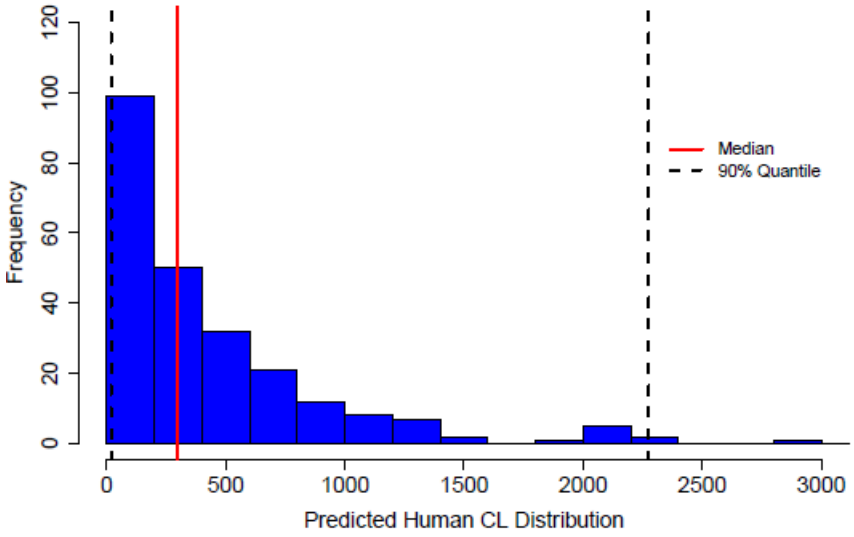


b.



2) Final model predicted human CLs distribution

c.



d.

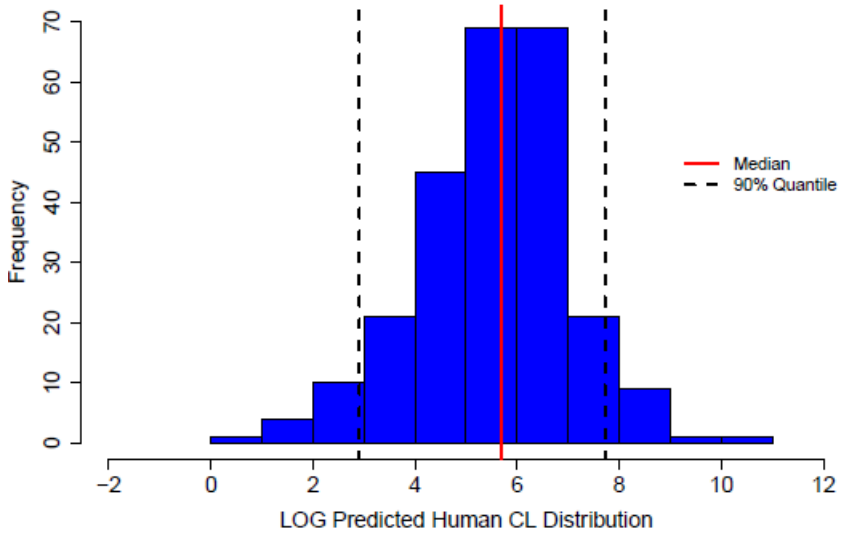
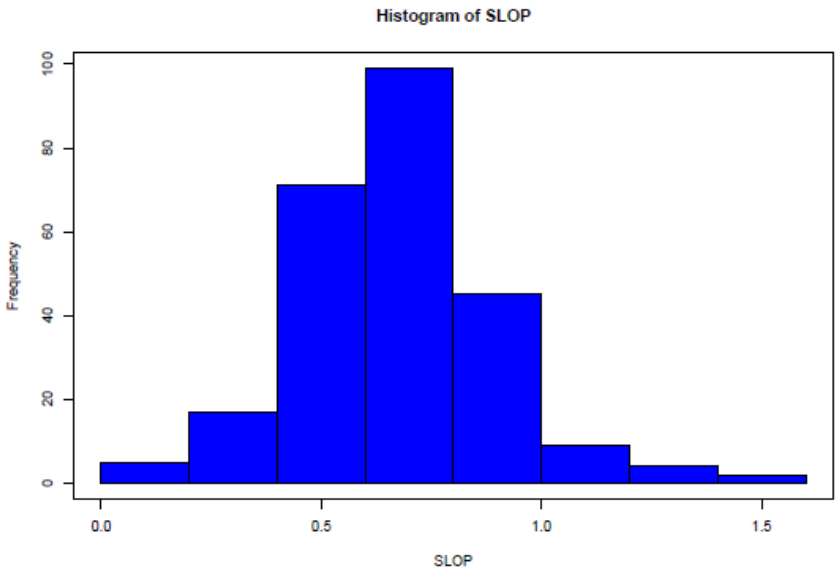
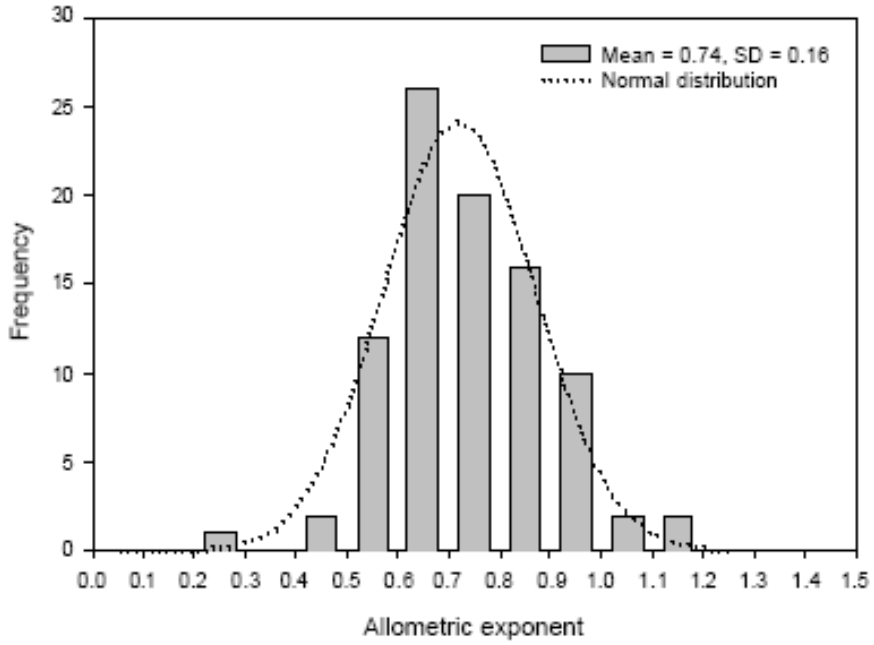


Figure 4. Distribution of Model Estimated AS Exponent versus Literature Reports

(A). Final model estimated AS exponent distribution (n = 251)



(B). Literature reported AS exponent distribution (n = 115)(38)



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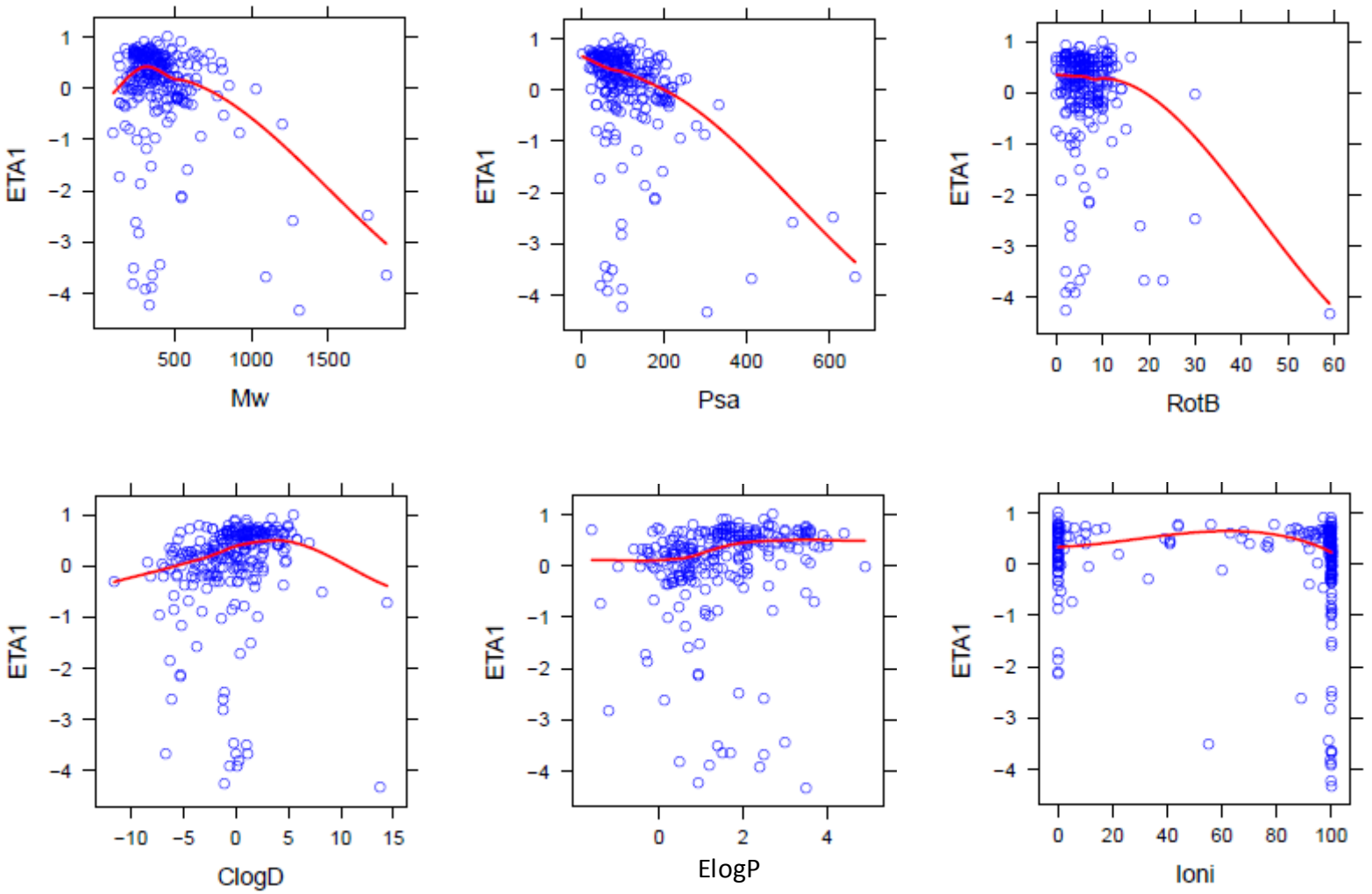
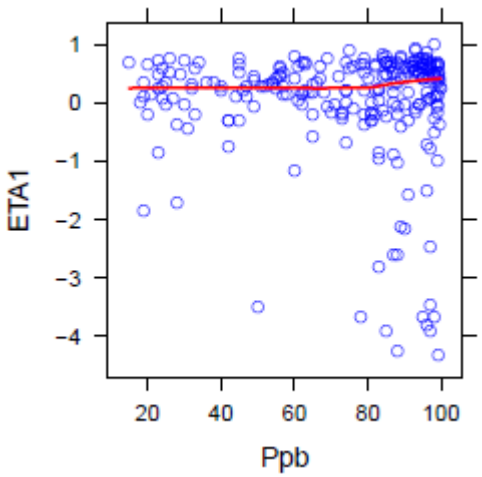
Appendix 1. Correlation between ETA1 and ETA2 with Potential Covariates

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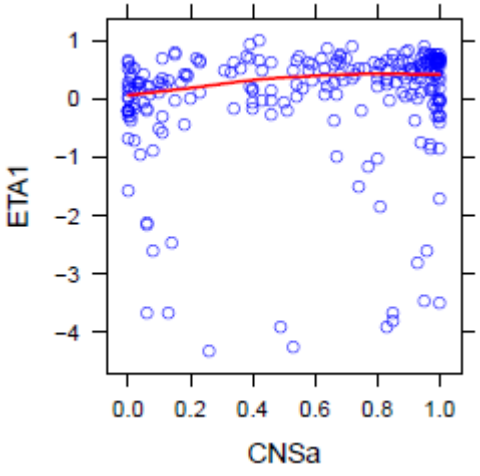
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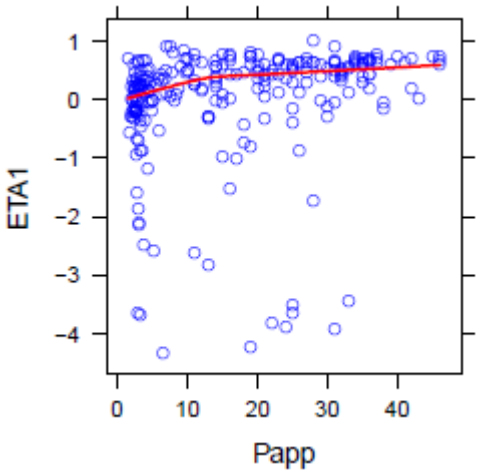
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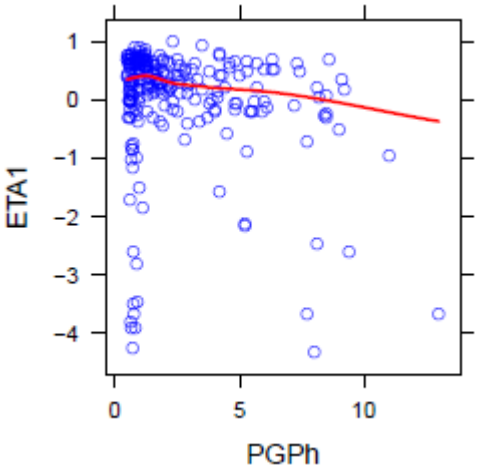
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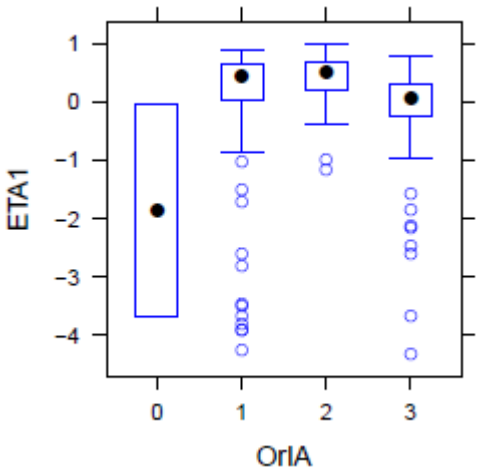
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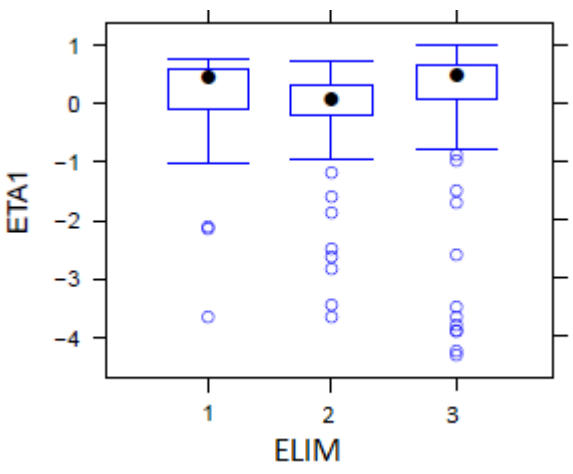
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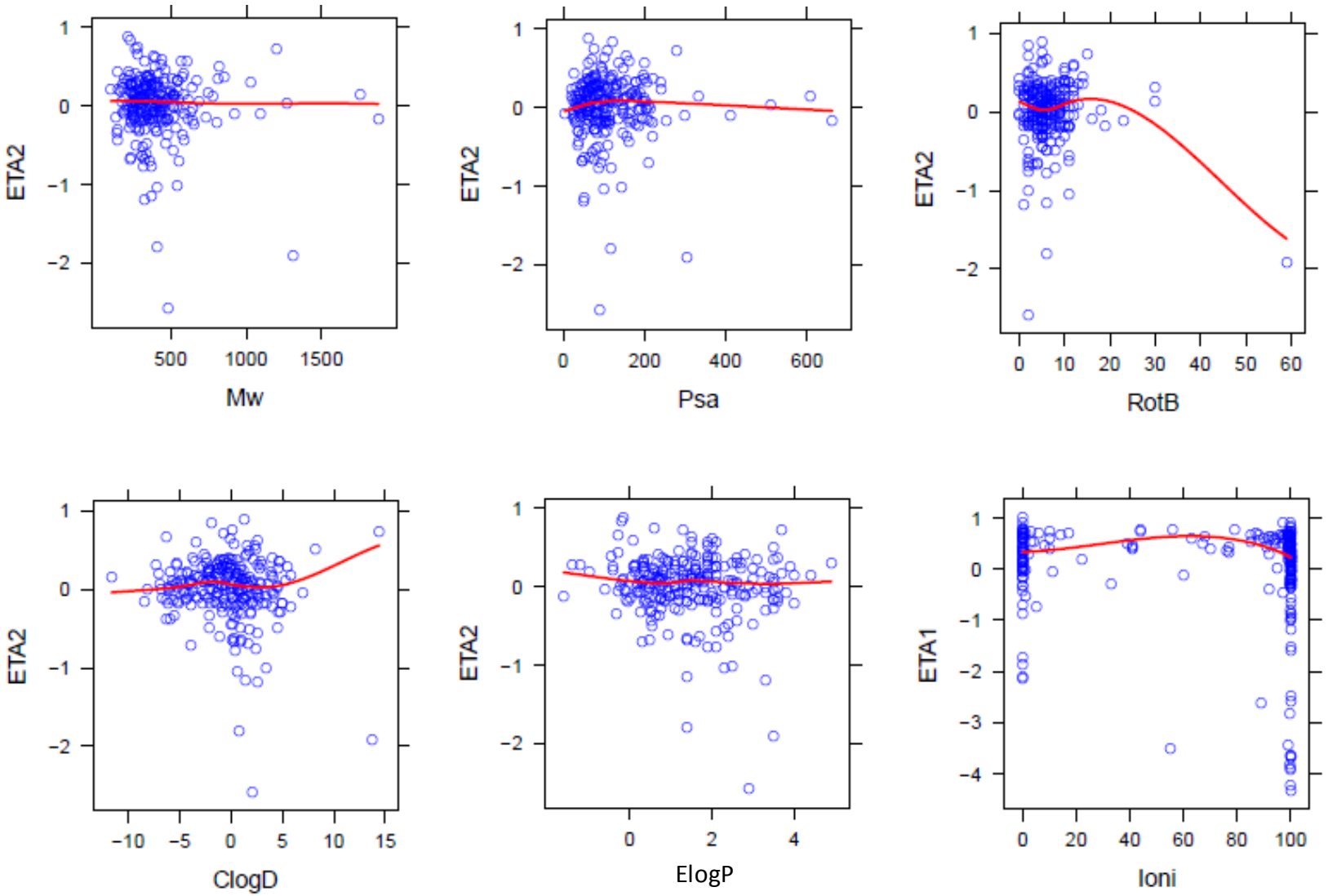
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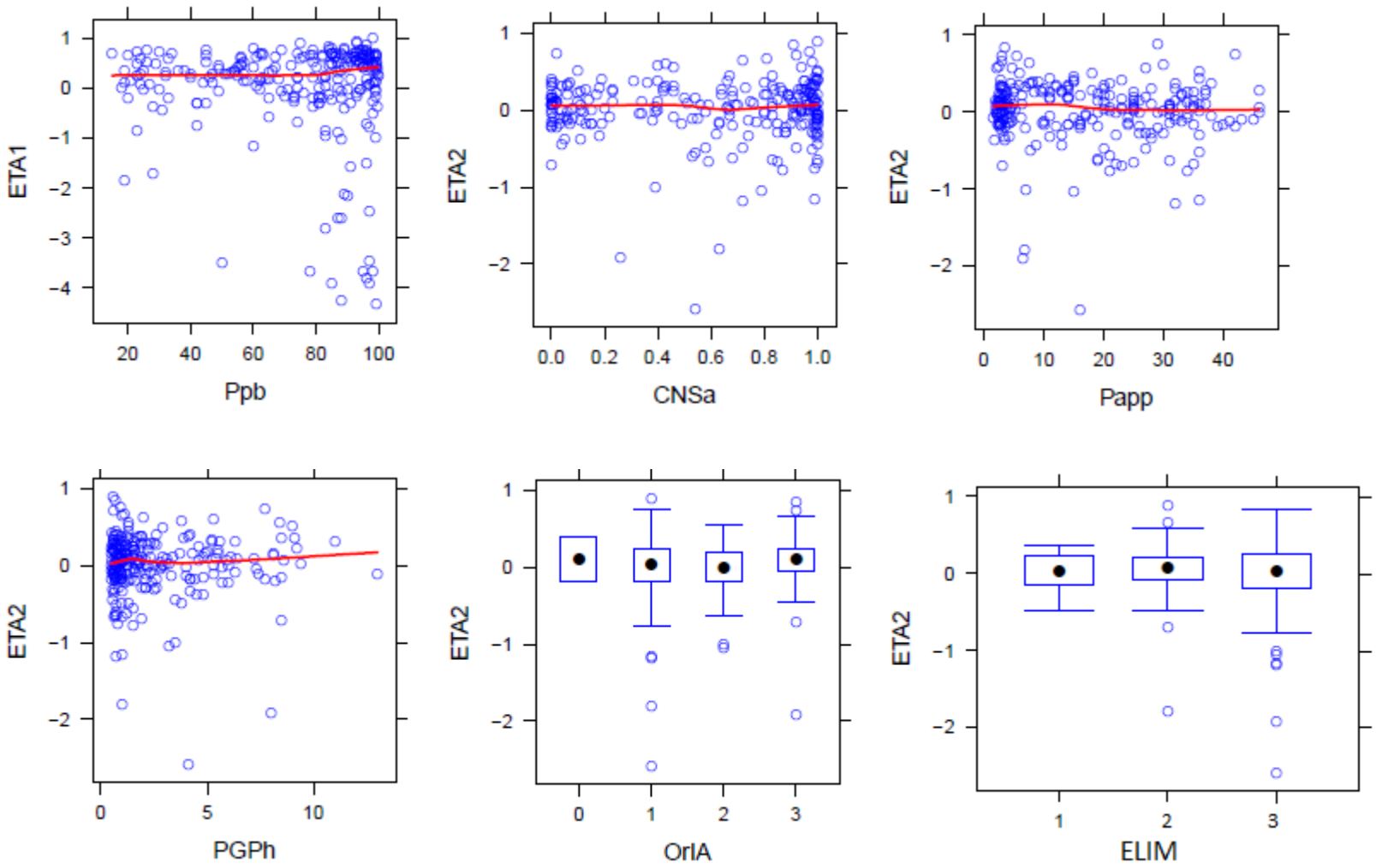
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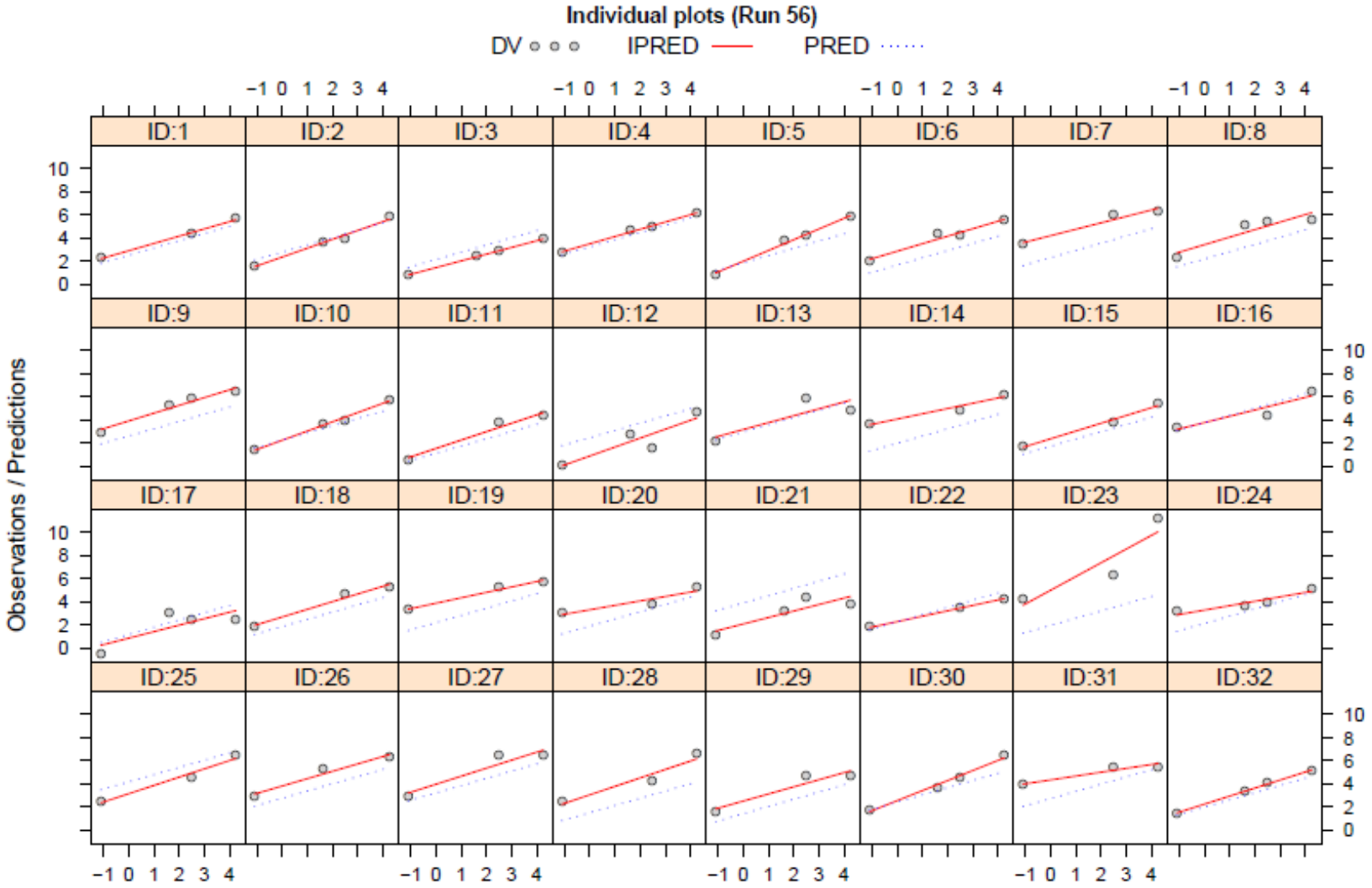
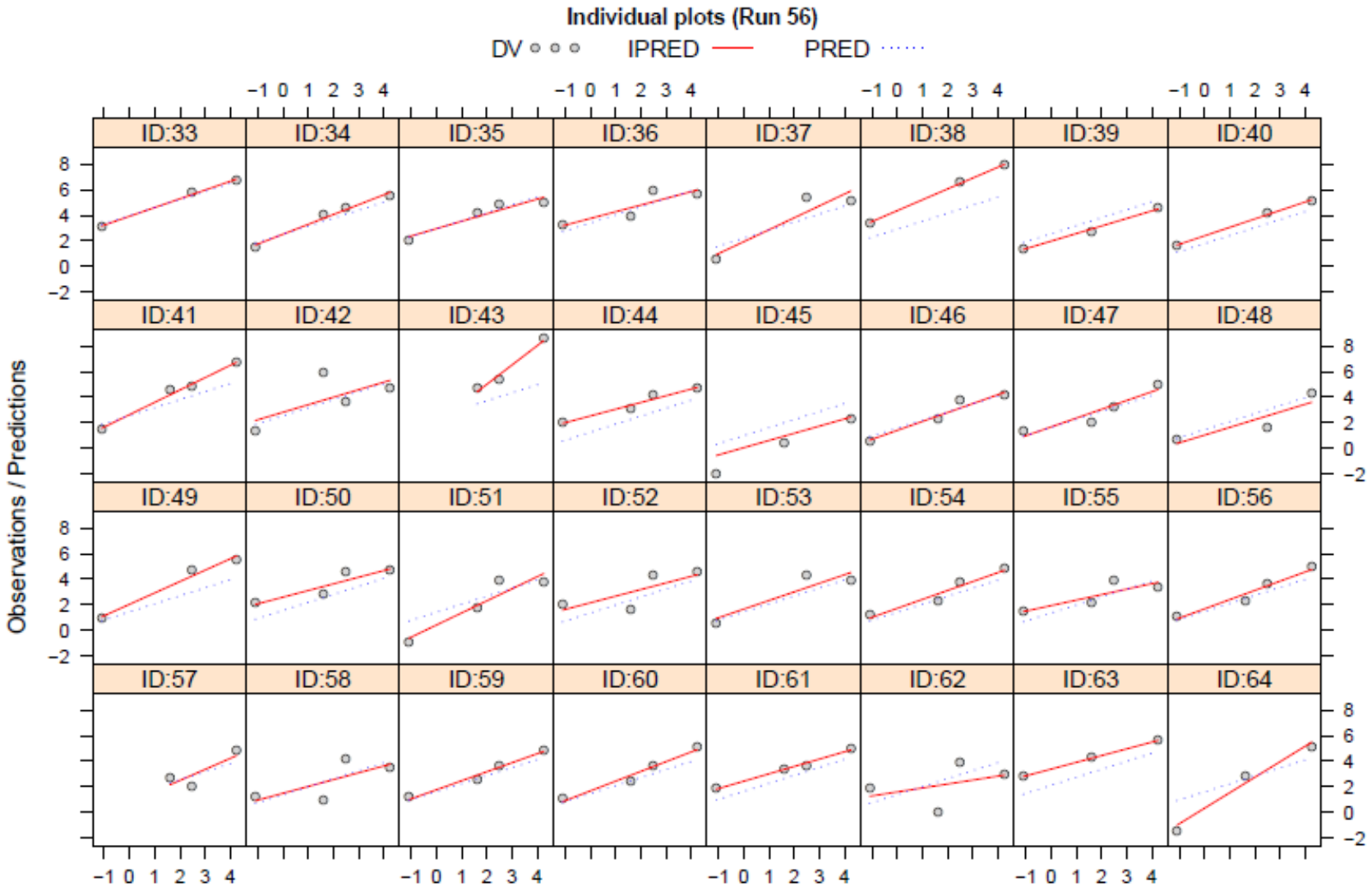
Appendix 2. Individual Drug Observed versus Model Predicted CLs Cross Species from the Final AS Model

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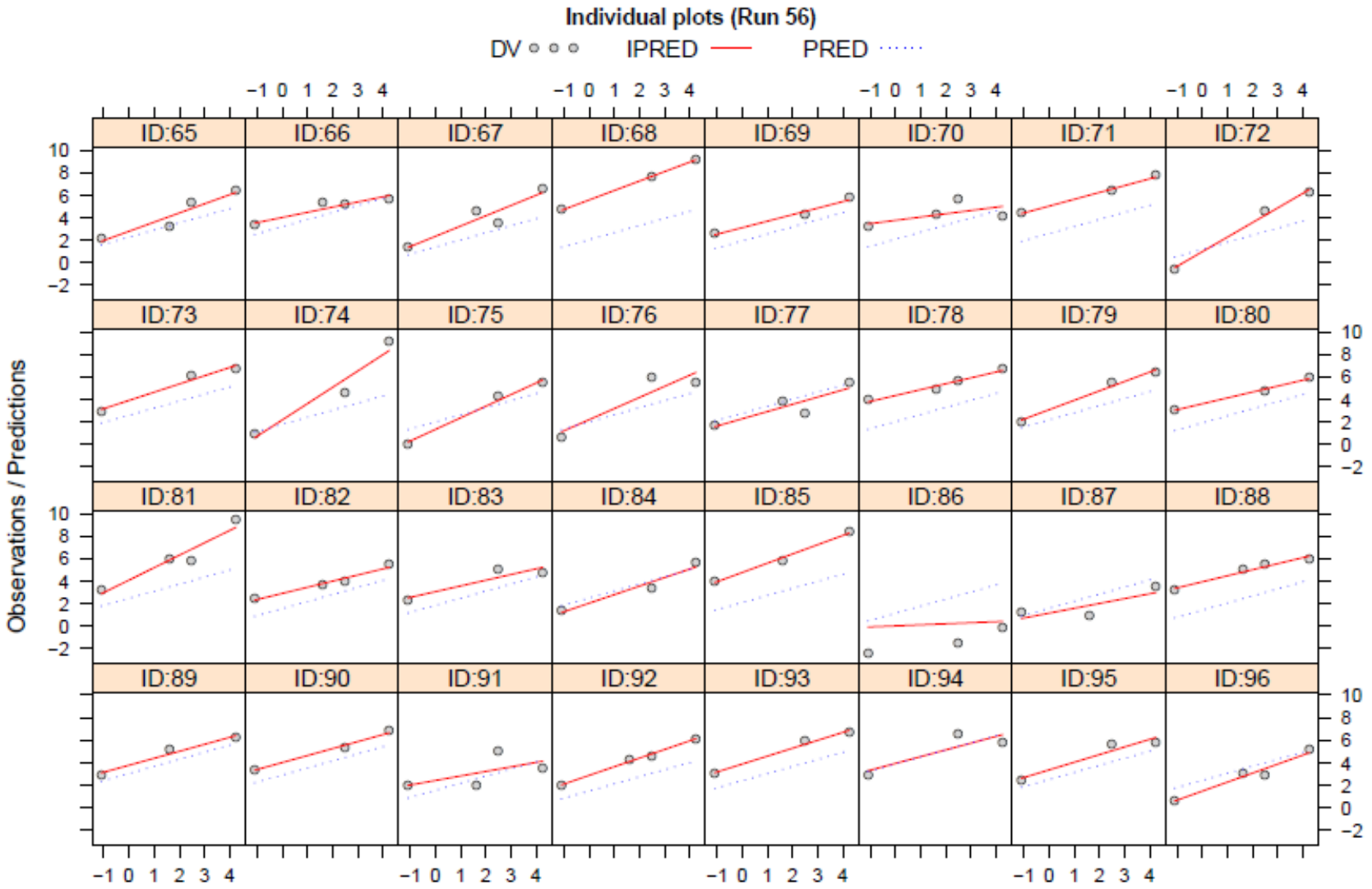
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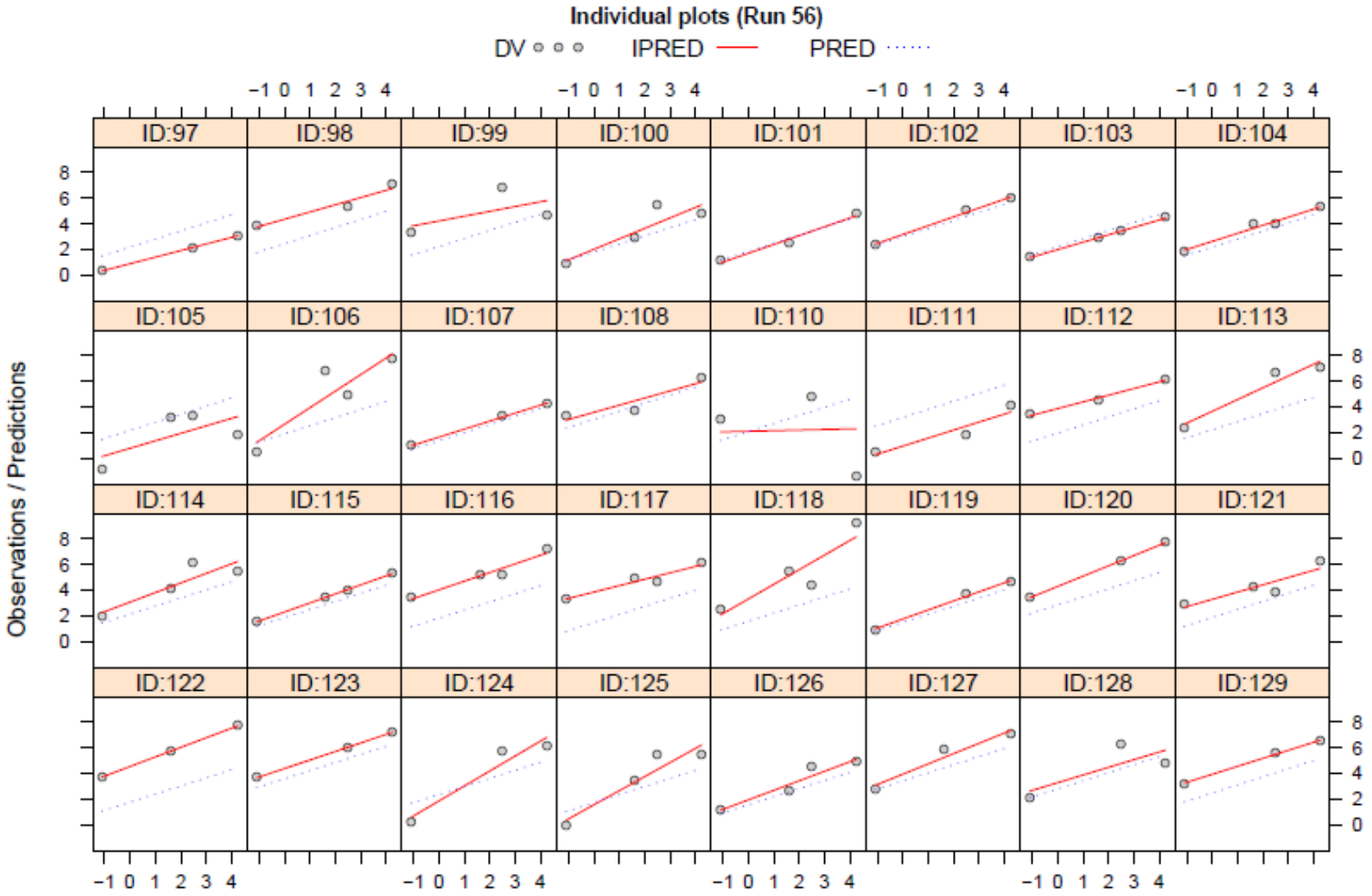
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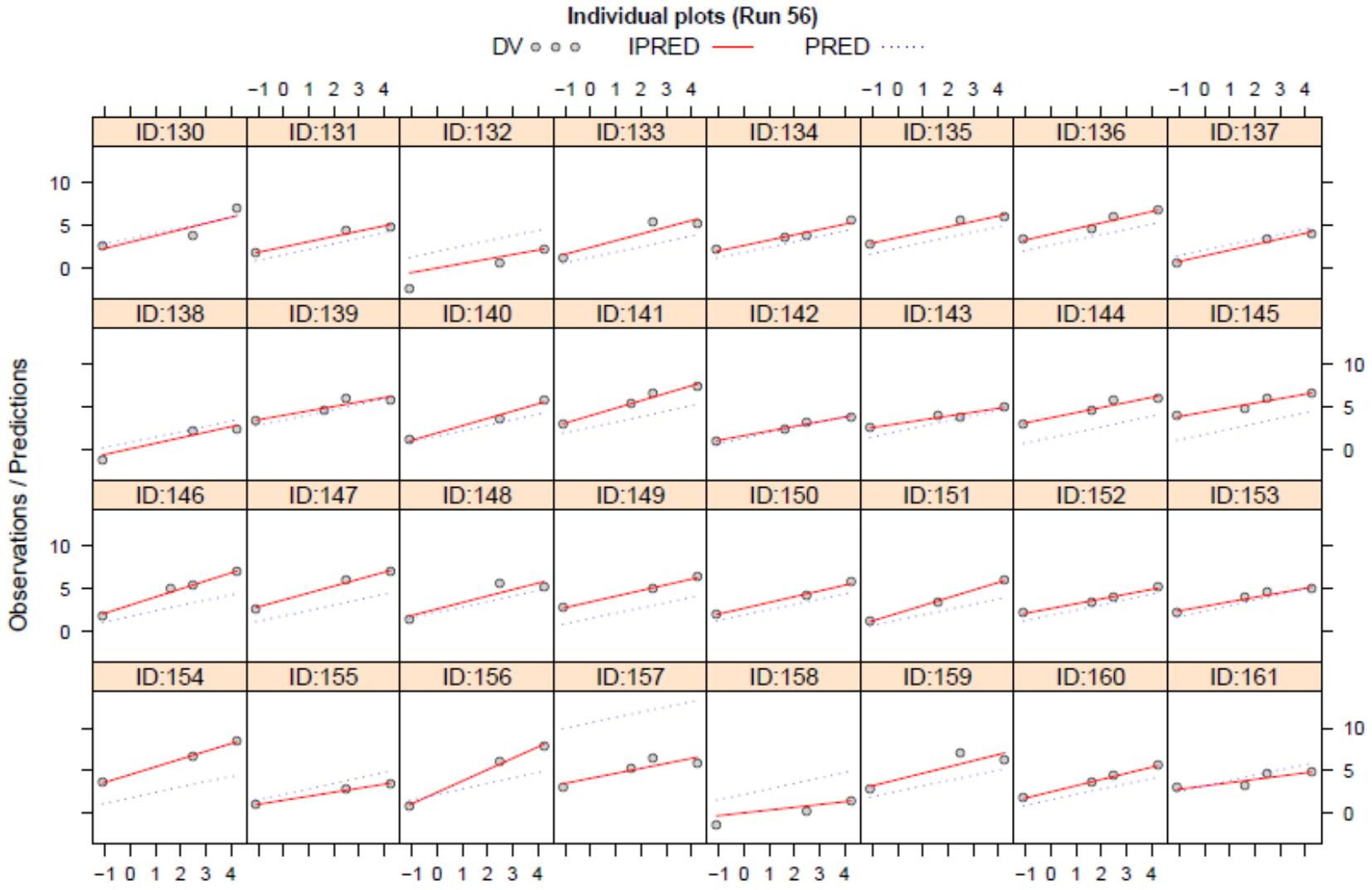
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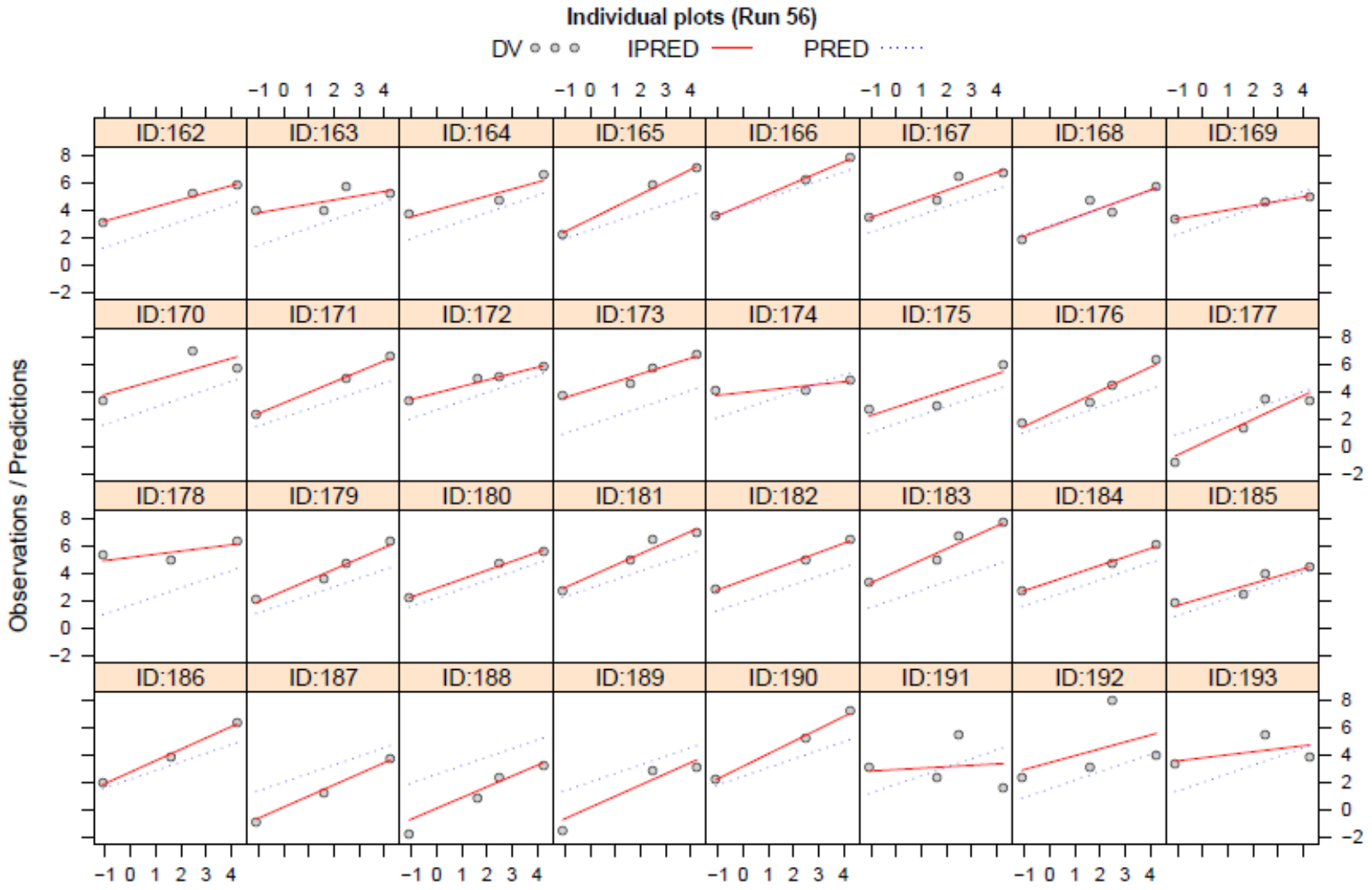
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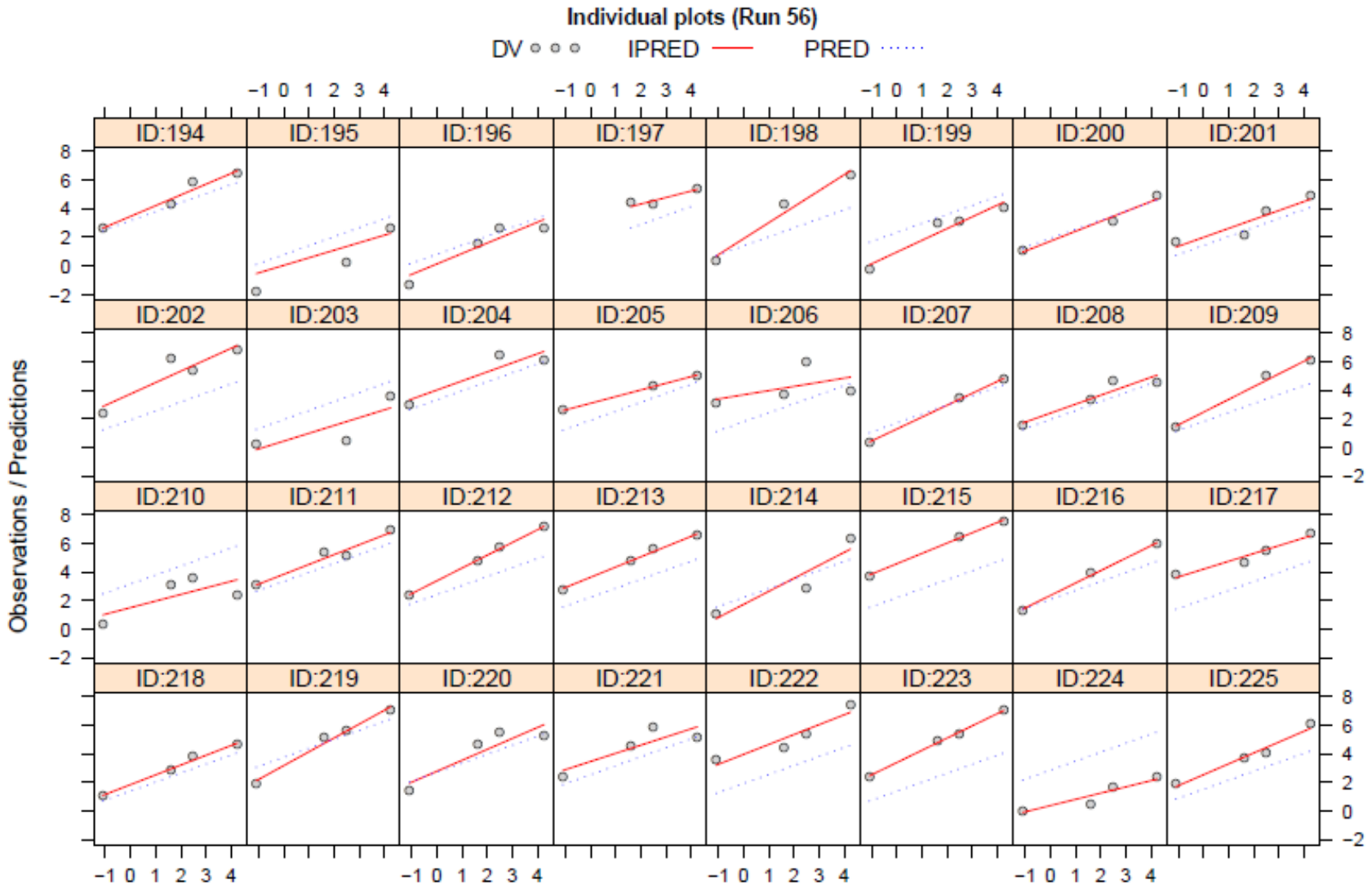
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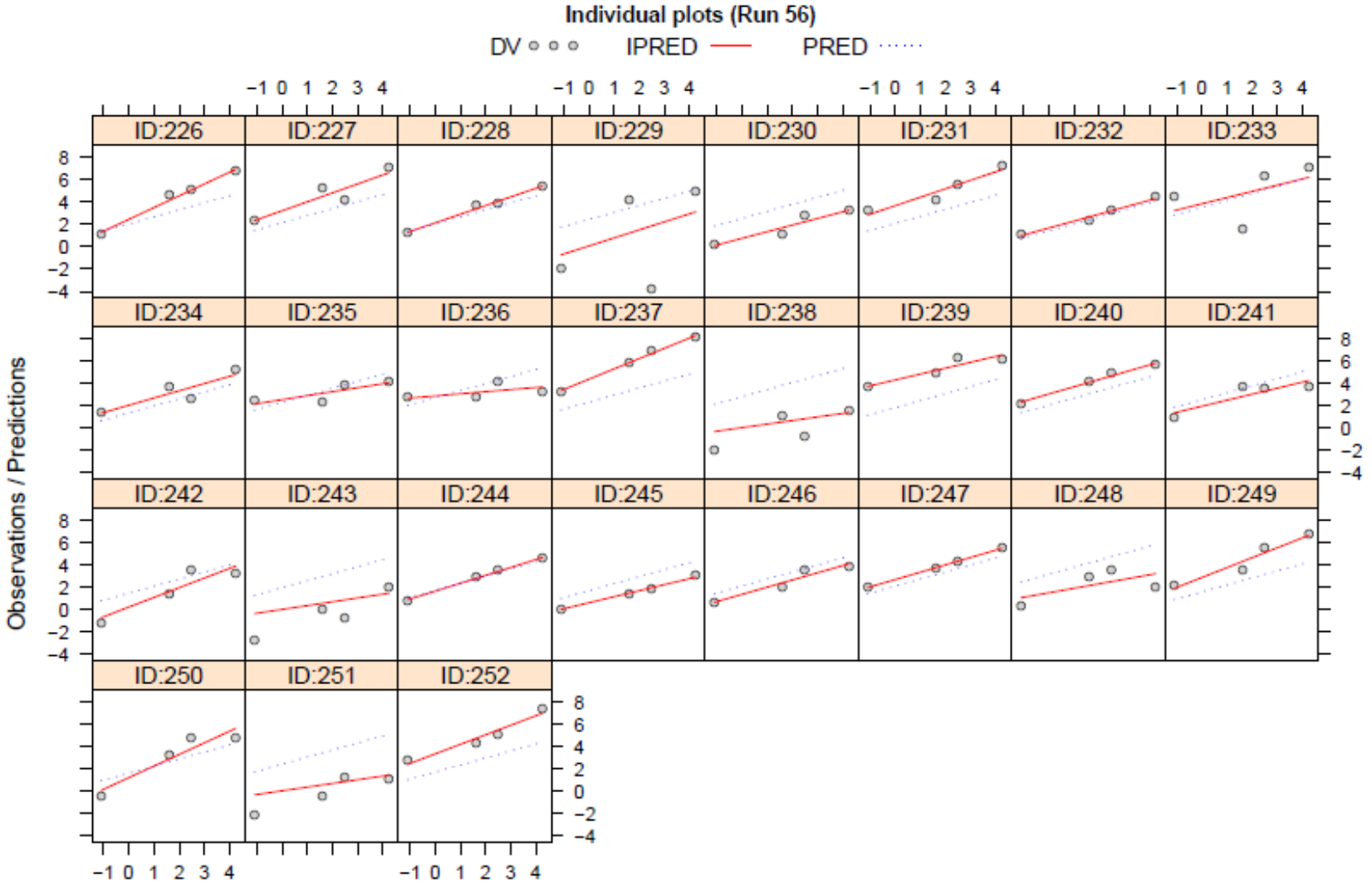
Individual plots (Run 56)
DV
IPRED
PRED
Observations / Predictions
ID:226
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ID:228
ID:229
ID:230
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ID:233
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ID:251
ID:252

Appendix 3. Final Model Control File

```
$PROB Allometric scaling exploration run56 ; run56.mod

$INPUT ID sub DV TIME MDV CNSa lgDH Papp Ppb PGPh OrlA Mw Psa RotB ClogD Ioni
ELIM1 ELIM2 ELIM3

$DATA AS.4.csv IGNORE = C

$PRED ; Calculate the prediction of the model
 ; COEF vs. Psa
   COEFPsa = (Psa/89)**THETA(3)

   TVCOEF=THETA(1)*COEFPsa

   TVSLOP=THETA(2)
   COEF = TVCOEF * EXP(ETA(1))
   SLOP = TVSLOP * EXP(ETA(2))

   F = COEF+SLOP*TIME
   IPRED = F
   IRES = EXP(DV) - EXP(F)
   IWRES = IRES/EXP(F)
   Y = F + ERR(1)

$THETA ; Starting estimates for the structural model
    (0, 1.3) ; COEF
    (0, 0.596) ; SLOP
    -0.3       ; COEFPsa

$OMEGA ;
    0.3302
    0.005

$SIGMA;
   0.03162 FIX

$ESTIMATION SIG=3 MAX=2000 PRINT=1 METHOD = 1; 3 significant digits, 2000
iterations max

$COV

$TABLE ID sub TIME DV MDV COEF SLOP ETA(1) ETA(2)CNSa lgDH Papp Ppb PGPh
Mw Psa RotB ClogD Ioni OrlA ELIM1 ELIM2 ELIM3 NOPRINT ONEHEADER
FILE=patab56
```

$TABLE ID sub TIME DV MDV COEF SLOP CNSa lgDH Papp Ppb PGPh Mw Psa RotB ClogD Ioni ONEHEADER FILE=cotab56 NOPRINT

$TABLE ID sub TIME DV MDV COEF SLOP OrlA ELIM1 ELIM2 ELIM3 ONEHEADER FILE=catab56 NOPRINT

$TABLE ID sub TIME DV MDV COEF SLOP IPRED IWRES CWRES IRES ONEHEADER FILE=sdtab56 NOPRINT

$TABLE ID sub TIME DV MDV COEF SLOP ETA(1) ETA(2) IPRED IWRES CWRES IRES CNSa lgDH Papp Ppb PGPh Mw Psa RotB ClogD Ioni OrlA ELIM1 ELIM2 ELIM3 ONEHEADER FILE=alltab56 NOPRINT

CHAPTER 3

MODELING AND SIMULATION APPROACH FOR CHARACTERIZING AND EVALUATING THE SINGLE SPECIES ALLOMETIC SCALING

1_Abstract

Objective: Animal and human systemic clearance (CL) data were collected and used for the characterization and evaluation of single species allometric scaling (AS). Potential effects of drug physicochemical and pharmacokinetic (DMPK) properties on the estimated single species AS exponents were also investigated.

Methods: Single species AS was characterized using extensive literature collected data to estimate the single species AS exponent distribution and central tendency. Comparisons of single species AS exponent estimates based on different species and commonly reported values were conducted. Correlations were investigated between the estimated AS exponents and the physicochemical and pharmacokinetics (DMPK) properties of the compounds examined. For a hypothetical compound under drug development, stochastic simulations, based on the uncertainty obtained from the data and modeling results from this work, were performed in order to capture the uncertainty in the predictions of human CL from single species methods.

Results: The estimated single species AS exponents were consistent with literature reports and the commonly used exponent values. There were no obvious correlations identified between the estimated AS exponents and the physicochemical properties or pharmacokinetics (DMPK) properties of the compounds. This analysis utilizing a large data set increased the confidence in applying the exponents of single species methods. Further, it offers robust estimates on the uncertainties, which should be incorporated in the practice of single species allometry.

2_Introduction

During drug development, interspecies scaling is a commonly used tool to predict pharmacokinetic parameters in humans from animal data and for the first in man dose selection (1). Allometric scaling has become one of the most widely used approaches for human CL prediction based on measured animal species CL(2). Allometric scaling was developed based on the principle that the relationship between organ size, regional perfusion and body weight of mammals could be characterized by a simple power law expression, $Y = a W^b$, where W is species body weight, Y in this case is CL, and a and b are the allometric coefficient and exponent, respectively.

Because of the empirical nature of AS and the various reported prediction failures for human CL through AS, there have been a number of attempts to refine the simple AS to improve its predictability on human CL. The modification and correction methods to simple AS include using brain weight (BW) and maximum life span (MLP) corrections (2)(3) utilizing the "rule of exponents (ROE)", an empirical correction technique which lowers the prediction of human CL when a relatively high AS exponent is obtained through simple AS (4), *in vitro* metabolic CL

correction (5), correction for the unbound fraction of drug in plasma (6) and correction for plasma protein binding differences between animals and humans (7). The results of these correction factors on simple AS, however, have been controversial (5). The ROE method has gained substantial support and did improve human CL prediction in some cases. However, some researchers analyzing larger AS data sets reported that the ROE method provided no significant improvement for human CL predictions compared to simple AS (8)(9).

Along with the debates on the simple AS and its correction approaches, another major controversy in AS is whether to use varying-exponent allometry or fixed-exponent allometry (8-12). Interspecies scaling extrapolation based on the empirical power function whose exponent (and coefficient) estimated from animal data is termed varying exponent AS. This includes simple AS as well as AS with any modifications and correction factors. The limitations and intrinsic defects of this approach have been extensively discussed (3)(4)(5)(9)(13)(14). Tang and Mayersohn demonstrated that the functionality of applying correction factors in simple AS is essentially equivalent to multiplication of some predetermined constant values to the predicted human CL obtained from simple AS and has no bearing on PK parameter measurements in the animal species (15). Tang et al. further showed, from both mathematical/statistical theory and experimental data, that the varying-exponent AS approach or the utilization of various correction factors should not be employed in interspecies scaling of pharmacokinetic parameters (16). Currently, fixed-exponent AS is commonly used in the pharmaceutical industry. For scaling CL between adults and children, AS with a fixed exponent of 0.75 is often applied (17). Based on a data-driven approach, Tang and Mayersohn derived one and two species-based AS methods for human CL prediction using animal CL data. In their results, the single species AS methods demonstrated as $CL_{human}/kg = 0.152 \times CL_{rat}/kg$, $CL_{human}/kg = 0.410 \times CL_{dog}/kg$ and CL_{human}/kg

$= 0.407 \times CL_{monkey}/kg$, which mathematically were equivalent to exponents of 0.648, 0.494 and 0.659 for rat, dog and monkey single species AS methods with the assumption that the median body weights of human, rat, dog and monkey at 70 kg, 0.33 kg, 12 kg and 5 kg, respectively (10).

Generally AS methods have been developed based on relatively small sets of data (12). One common criticism of allometry is on its empiricism, which is heavily dependent on the data selection and sample size. Inconsistency and controversies among different allometric methods or models were partially due to the limited data sets that have been analyzed. One of the major purposes of this investigation was to evaluate the current single species methods and to propose new models based on the analysis of a larger data set. In this study, single species AS was performed using a large diverse literature (n = 251) data set (in rat, dog, monkey and human) of CL values, and the AS exponents were estimated for single species AS predictions of human CL based on rat, dog or monkey DMPK data. The derived single species AS exponent distribution and central tendency was compared with commonly used single species AS exponents. In order to obtain possible explanations for the large inter-compound AS exponent variability, potential correlations between the estimated single species AS exponents versus the corresponding physicochemical and DMPK properties of drugs were investigated. For a hypothetical compound under drug development, simulations were performed for human CL prediction by incorporating the central tendency and uncertainties derived from this analysis.

3_Methods

Data collection

Two hundred and fifty one sets of intravenous administered drug systemic CL data were collected from the literature. The two-dimensional physicochemical and topological descriptors of the collected compounds were computed with an in-house program (Chemoinformatics, Monika Five v 1.2), which predicts physicochemical and pharmacokinetic properties based on chemical structures. After initial screening and correlation exploration, a total of 12 physicochemical and drug metabolism and pharmacokinetics properties of drugs were selected for the correlation investigation with the estimated single species AS exponents. The physicochemical and pharmacokinetic properties of drugs were: 1) molecular weight (MW); 2) polar surface area (PSA); 3) rotatable carbon bond (RCB); 4) calculated logarithm of the octanol-water partition coefficient (cLogP); 5) calculated logarithm of the octanol-water distribution coefficient (clogD; 6) ionization status (%IONI); 7) oral absorption property (good, moderate, bad) (OrlA); 8) plasma protein binding (PPB); 9) central nervous system absorption (CNSa); 10) apparent permeability through cell membranes (Papp); 11) human P-glycoprotein transporting property (PGPh); 12) elimination pathway (by metabolism; by renal elimination; by both) (ELIM). These parameters are defined and discussed in Chapter 2. Out of the 251 drugs data set, three separate data sets were extracted: CL in rat (CL_{rat}) versus CL in human (CL_{human}), CL in dog (CL_{dog}) versus CL in human (CL_{human}), and CL in monkey (CL_{monkey}) versus CL in human (CL_{human}). In each of the extracted data sets, the corresponding physicochemical and DMPK properties for each drug were carried along into the newly compiled data sets.

Single species AS

For each single species AS data set, CLs of each compound were plotted against its corresponding animal/human body weights on a log-log scale according the following AS equation:

$$\log CL = \log a + logW \qquad (1)$$

where W is body weight, and a and b are the coefficient and exponent, respectively. In this study, the CL in different species were assumed commonly used body weight of 0.33 kg, 12 kg, 5 kg and 70 kg for rat, dog monkey and human, respectively. Derived from the simple AS equation, the following equation was utilized to calculate the single species AS exponent (slope) for each drug, taking rat versus human single species AS as an example:

$$b = \frac{\log(CL_h) - \log(CL_r)}{\log(W_h) - \log(W_r)} \qquad (2)$$

where, b is the single species AS exponent (slope), CL_{human} and CL_{rat} are the observed human and rat CL, and W_{human} and W_{rat} represent body weight in human and rat, respectively.

Three single species allometric methods were obtained, namely rat, dog and monkey single species fixed allometry. The central tendency and distribution of the estimated exponent from each method were estimated and compared with the literature reported and commonly used one AS species exponent values. Descriptive statistical analysis of three sets of AS exponent estimations was conducted for mean, median and ranges by using software R 2.8.1.

Correlation between AS Exponent and Physicochemical and DMPK properties

The exponents from each method were first plotted against each estimated physicochemical and DMPK properties (potential covariate) to identify possible correlations. As a further evaluation, potential correlation between exponent (b) and each continuous potential covariate was tested by significant test in a linear regression model at the 0.001 significance level. For a categorical covariate, the estimated exponents for different drugs were grouped by the categorical covariate. One way analysis of variance (ANOVA) was thereafter employed to test the difference between grouped exponents. A p-value < 0.001 was considered statistically significant.

Simulations for Human CL Prediction

In order to demonstrate the practical utility of the single species AS approaches developed in this study, a hypothetical drug was proposed for each single species AS method. Hypothetical drugs with assumed mean CLs of 7.59, 103, and 39.8 mL/min for rats, dogs and monkeys, respectively, were used for further simulation. Those assumed CL_{rat} , CL_{dog} and CL_{monkey} were the corresponding median CLs of rat, dog and monkey estimated form the original data set. For each single species AS approach, Monte-Carlo simulation (n = 10,000) of exponents was performed based on the estimated exponent distribution, which was assumed to be normal distributed, N (mean, SD), where mean and SD were the average exponent and standard deviation. Taking rat single species AS as an example and based on the following derived equation (3) from the simple AS:

$$CL_{human} = CL_{rat} \times \left(\frac{W_{human}}{W_{rat}}\right)^{b} \qquad (3)$$

where, *b* is the single species AS exponent (slope) . For each single species method, 10,000 human CLs were thereafter predicted. The simulations were performed in R (R version 2.11.1). The distribution of the predicted human CLs based on different single species AS methods were illustrated in histogram plots. At the same time, as a further distribution exploration, the predicted CLs were also log transformed and plotted in linear scale using R program.

4_Results and Discussion

Within the main data set (n = 251), there were 249 drugs having both rat and human data; 231 having both dog and human CL values; 156 having both monkey and human CL values. These three extracted data sets, CL_{rat} versus CL_{human}, CL_{dog} versus CL_{human} and CL_{monkey} versus CL_{human} data sets, were utilized for the estimation of the single species AS exponent for each drug in each approach. The distributions and central tendencies of AS exponents for each single species AS method were demonstrated in **Figure 1.** The statistics of the exponent distributions are shown in **Table 1.** The mean rat single species AS exponent in this study was estimated to be 0.667, which was consistent with the previously reported rat single species AS exponent (0.66) based on 54 extensively metabolized drugs (12). Tang and Mayersohn, using a data driven (n = 102) statistical optimization approach (by minimizing the objective function of average absolute fold-error and optimizing the objective function of average fold-error at 1), derived single species methods for predicting human drug CL using animal CL from rat, dog and monkey. In their results the single species AS exponents were mathematically equal to 0.647, 0.494 and 0.659 for rat, dog and monkey single species AS approaches, respectively. Their results were very close to the mean exponents established in the present study with rat, dog and monkey single species AS exponents estimated at 0.667, 0.519 and 0.659, respectively. Although Tang and Mayersohn's data (N = 102) and the data in this work shared some common drugs, the data size in this work

was larger, thus, the results from the current study have provided solid evidence and greatly strengthen the usage of the widely accepted single species AS exponents. Interestingly, the exponents for the rat and monkey method showed relatively smaller inter-compound variability than that for the dog method.

Correlation between the three sets of AS exponents versus potential covariates (the estimated physicochemical and DMPK properties of the selected compounds) were inspected by visual exploration as well as statistical tests. The results are presented in **Table 2** and **Appendix 1.** For the visual inspections, there were no obvious correlations identified for any pair of a potential covariate with a single species AS exponent. Through the statistical tests, there was no statistically significant correlation (for continuous potential covariates) or any significant difference among groups (categorical covariates) (P-value < 0.001). Considering the size and diversity of the collected literature data, it is not very likely that these physicochemical properties play a role in AS. Mechanistically, with the exception of renal filtration, clearance is mainly governed by biochemical processes such as enzymatic biotransformation and transporter mediated transportation. Renal reabsorption is largely dependent on plasma drug-protein binding and permeability. The current physiochemical properties analyzed may be more relevant to the distribution rather than the elimination of chemicals. This is consistent with the well-recognized facts that volume of distribution may be well predicted purely based on physiochemical properties (18) while for CL, there have been few successful reports with *in silico* approaches (19).

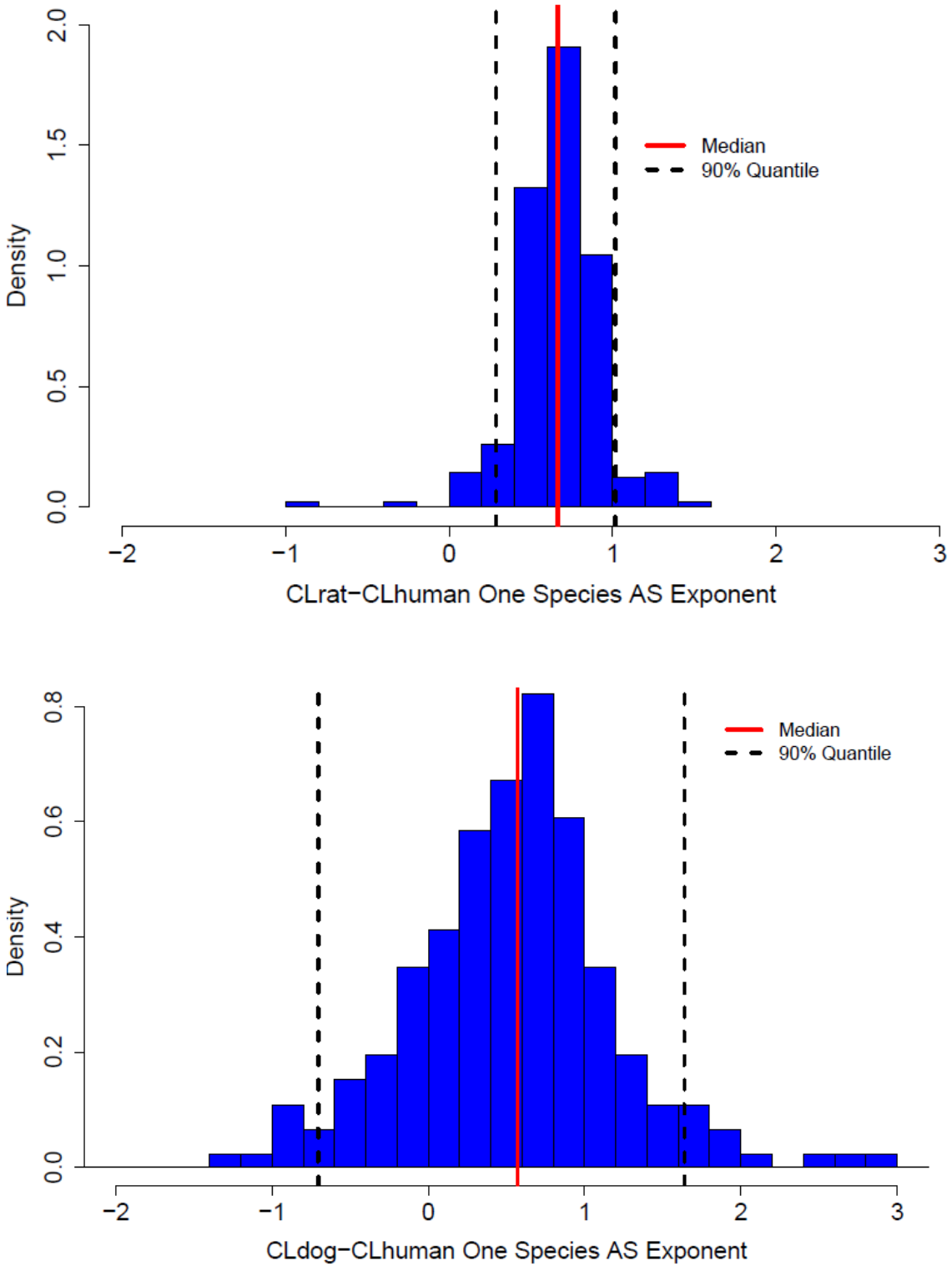
To further explore the practical application of the current developed single species AS models, Monte Carlo simulations were performed for each single species AS approach to predict human CL for a hypothetical drug, in order to capture the uncertainties of the human CL predictions.

Based on the exponent and their distributions estimated in this study for rat, dog and monkey single species AS method: N (0.667, 0.25), N (0.519, 0.80) and N (0.659, 0.36), respectively, 10,000 exponents were simulated for each approach. Thus, for a hypothetical drug with a mean drug CL of 7.59 ml/min, 103.2 ml/min and 39.8 ml/min for rat CL, dog CL and monkey CL, respectively, 10,000 corresponding human CLs were thereafter estimated for each single species AS approach. The predicted human CL distributions were demonstrated in the in **Figures 2, 3** and **4.** For all three methods, the predicted human CLs were log transformed and plotted in linear scale. As expected, the predicted human CLs followed a log normal distribution. All three methods are associated with relatively large uncertainty in predicted clearance values. The median predicted human CL based on rat, dog and monkey methods, was 268.2 ml/min with 90% quantiles at 29.2 – 2385.2 ml/min, 258.3 ml/min with 90% quantiles at 26.5 – 2649.8 ml/hr, and 226.2 ml/min with 90% at 44.9 – 1083.1 ml/hr, respectively. For the rat, dog and monkey single species AS approaches, the ratios of 95% to 5% human CL prediction are 81.8, 110.1 and 24.1, respectively. Monkey single species AS approach showed the narrowest human CL prediction ranges and appeared to have better predictability compared to rat and dog single species AS.

Typical allometry analyses reported one-number prediction without acknowledgement of prediction uncertainty. This type of individual and retrospective analysis misses an important part of the prediction sciences, which is the uncertainty. In reality, the uncertainty exists for all CL predictions given the empirical nature of allometry scaling, therefore, uncertainty in prediction should be incorporated into the predictions. The current investigation provides a framework and quantitation of these uncertainties for the single species AS, thus representing a realistic risk assessment and creating a scientifically sound decision-making avenue in human PK and dose prediction. It is noteworthy that the uncertainty for the monkey method appeared to

be the smallest. This probably makes sense in term of species proximity of monkey to humans; thus, the biochemical processes may be most similar to those in humans. Other research also suggested this (9)(10).

Figure 1. Single species AS exponent central tendency and distributions based on literature collected data of CL_{rat}-CL_{human} (n = 249), CL_{dog}-CL_{human} (n = 231) and CL_{monkey}-CL_{human} (n = 156)



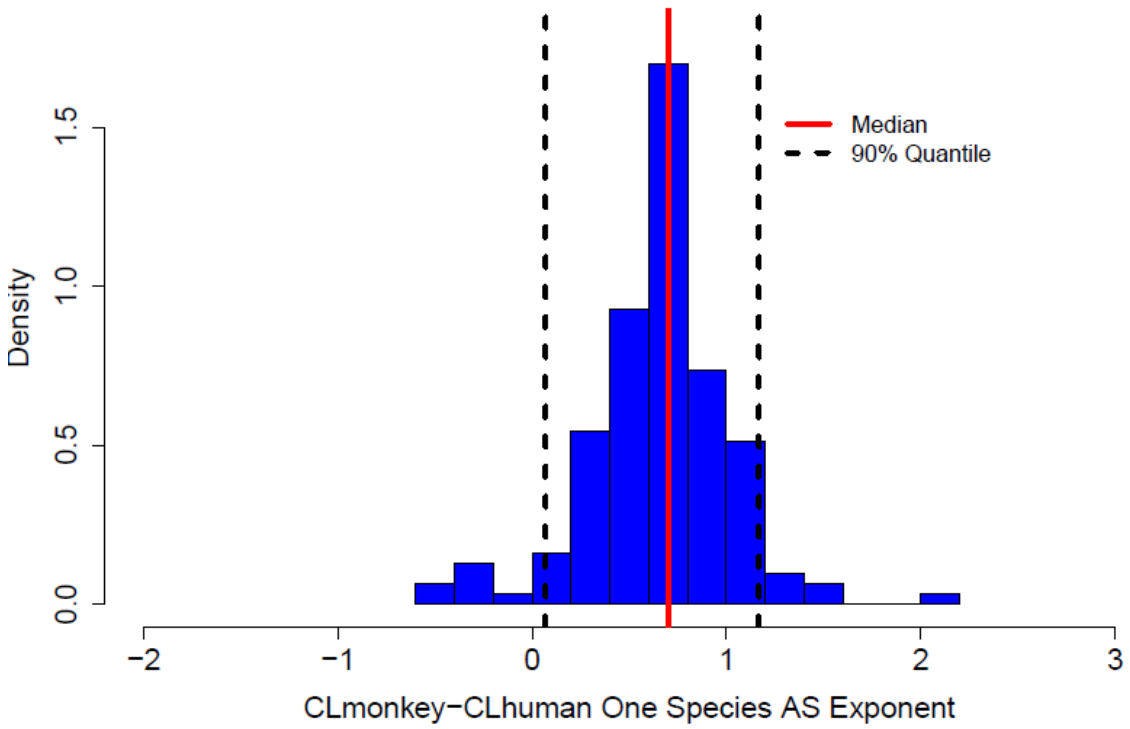

Median
90% Quantile
Density
0.0
0.5
1.0
1.5
−2
−1
0
1
2
3
CLmonkey−CLhuman One Species AS Exponent

Figure 2. Distributions of predicted human CL (ml/min) values for 10,000 simulations based on rat single species AS approach. Linear scale and log-transformed scale are presented in upper and lower plots, respectively.

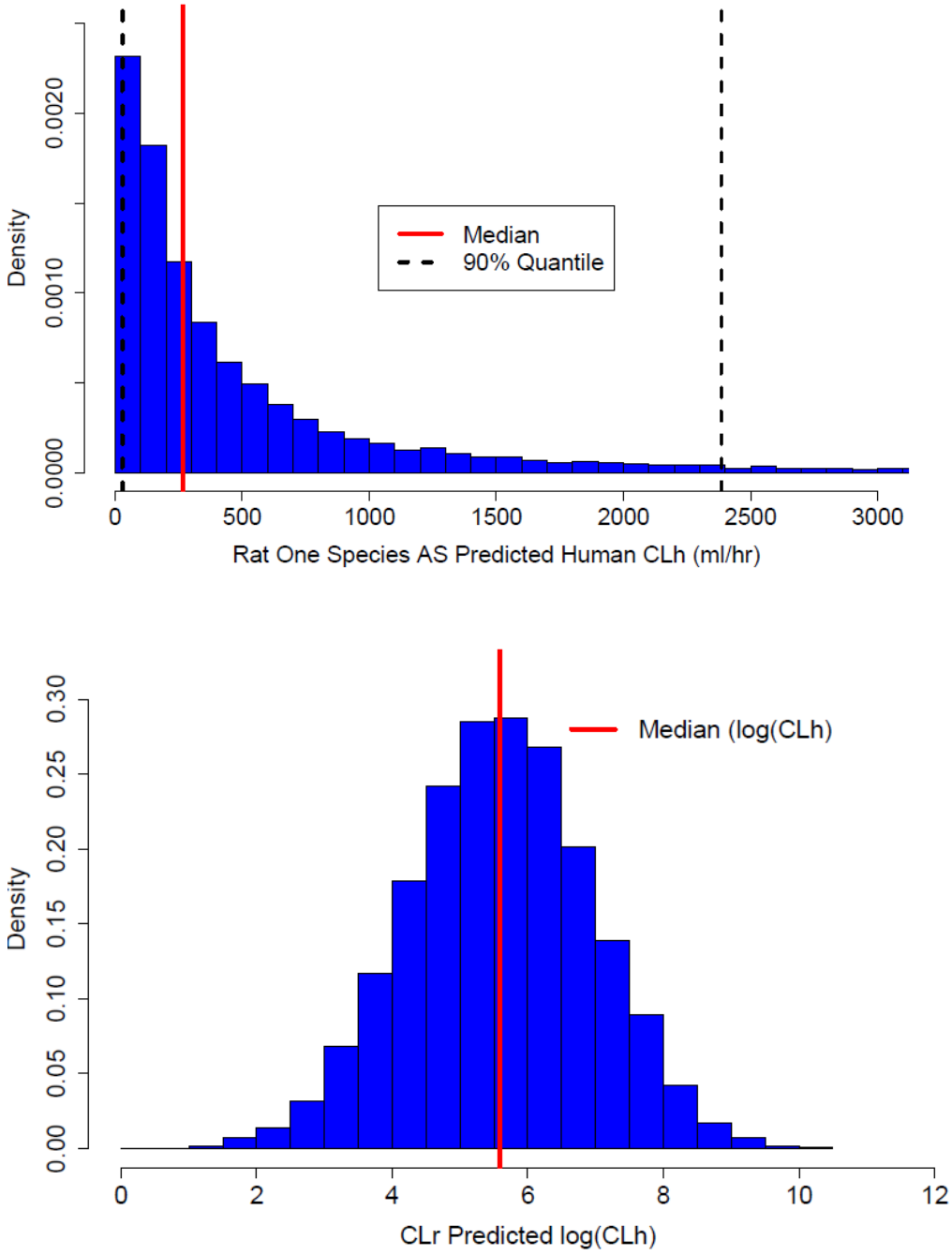


Figure 3. Distributions of predicted human CL (ml/min) for 10,000 simulations based on dog single species AS approach. Linear scale and log-transformed scale are presented in upper and lower plots, respectively.

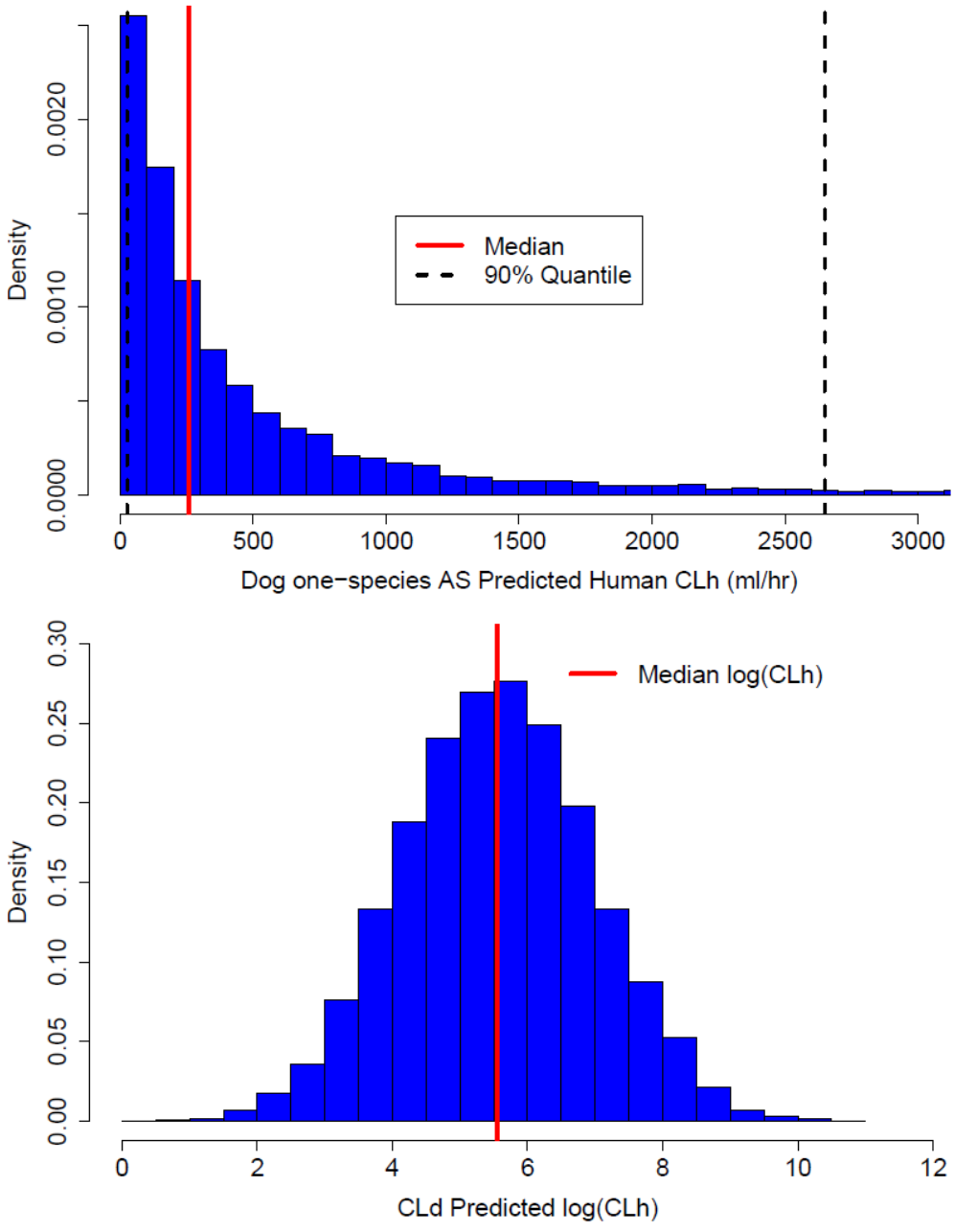


Figure 4. Distributions of predicted human CL (ml/min) for 10,000 simulations based on monkey single species AS approach. Linear scale and log-transformed scale are presented in upper and lower plots, respectively.

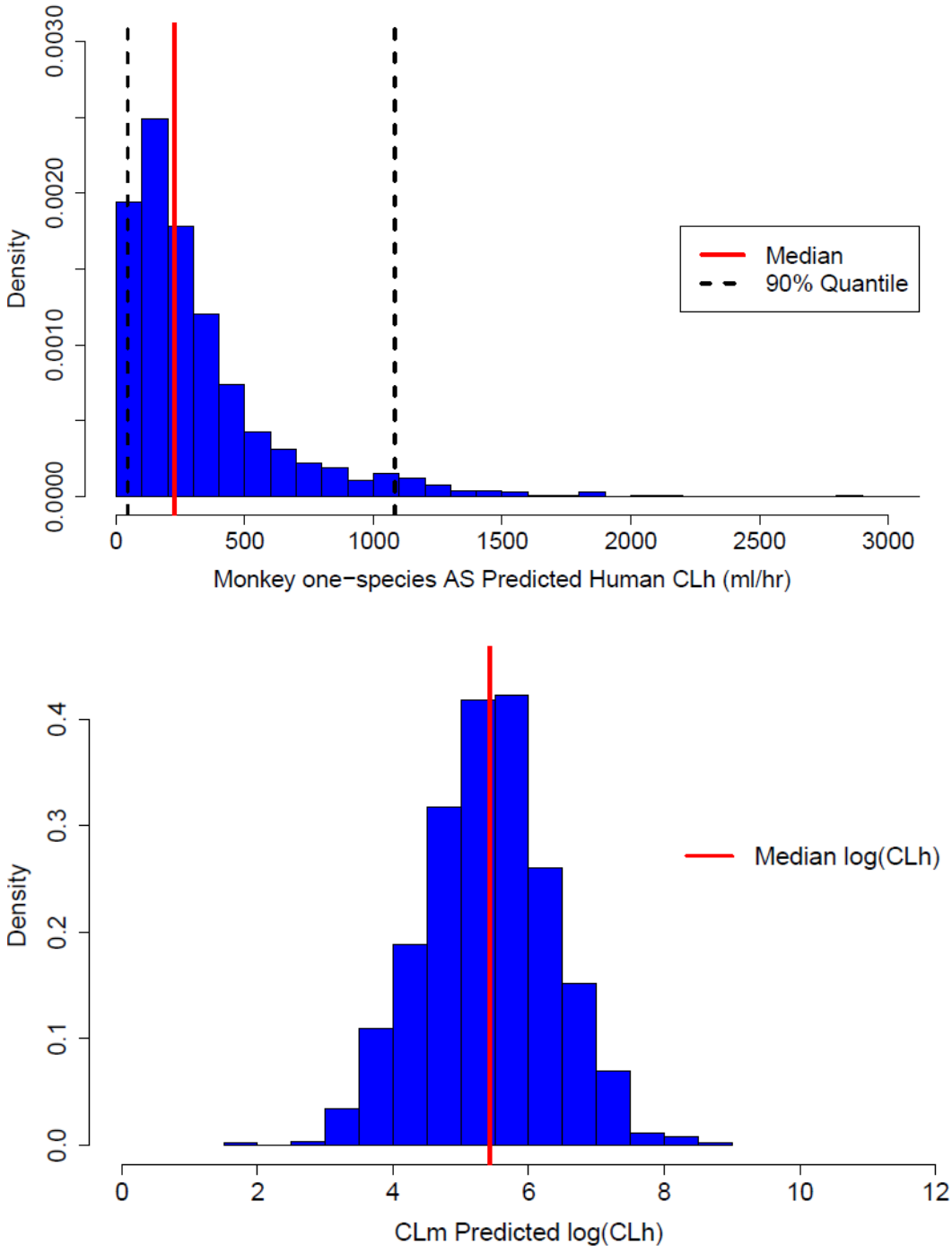


Table 1. Summary statistics of the estimated AS exponent distribution for single species AS rat, dog and monkey methods based on the literature data

	N	Mean	Median	Standard Deviation	Range
Rat AS Exponents	249	0.667	0.666	0.25	-0.83 – 1.53
Dog AS Exponents	231	0.519	0.570	0.80	-3.49 – 4.92
Monkey AS Exponents	156	0.659	0.701	0.36	-0.48 – 2.07

Table 2. Statistical analysis of the correlations of exponents from three different single species AS with the physicochemical and DMPK properties

		P - value		
	Physicochemical and DMPK properties	Rat versus Human	Dog versus Human	Monkey versus Human
Significant Test in Linear Regression	MW	0.839	0.303	0.700
	PSA	0.267	0.919	0.145
	RCB	0.863	0.915	0.064
	cLogP	0.076	0.008	0.032
	cLogD	0.852	0.083	0.039
	%ionized	0.124	0.768	0.902
	PPB	0.006	0.001	0.013
	CNSa	0.723	0.562	0.028
	Papp	0.118	0.280	0.048
	PGPh	0.977	0.297	0.022
One Way Analysis of Variance	OrlA	0.195	0.685	0.001
	ELIM	0.804	0.664	0.060

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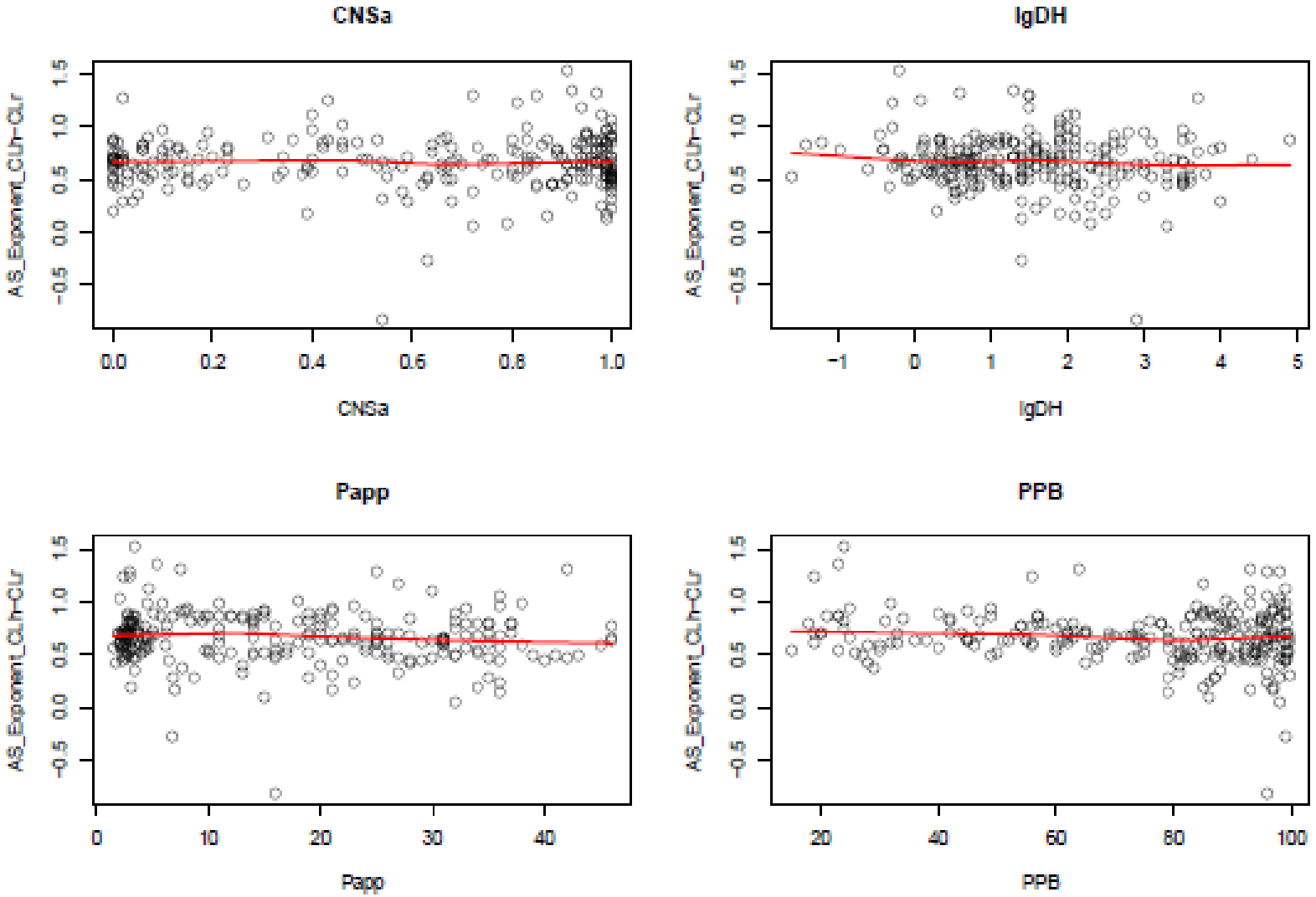
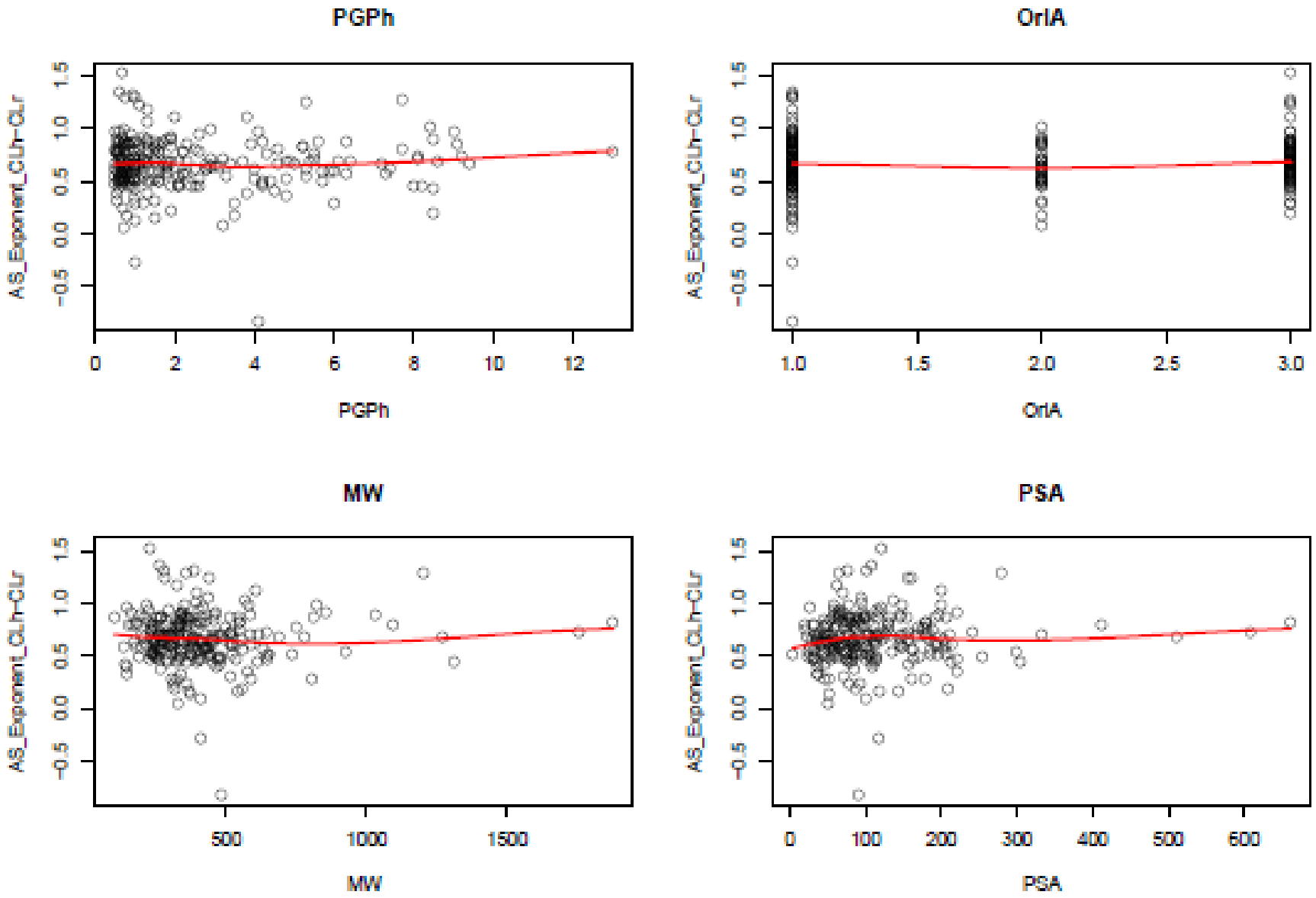
Appendix 1. The correlations between the single species AS exponents (from the CL_{rat} versus CL_{human}, CL_{dog} versus CL_{human}, CL_{monkey} versus CL_{human} data sets) with the estimated physicochemical and DMPK properties




PGPh
AS_Exponent_CLh-CLr
PGPh
OrlA
AS_Exponent_CLh-CLr
OrlA
MW
AS_Exponent_CLh-CLr
MW
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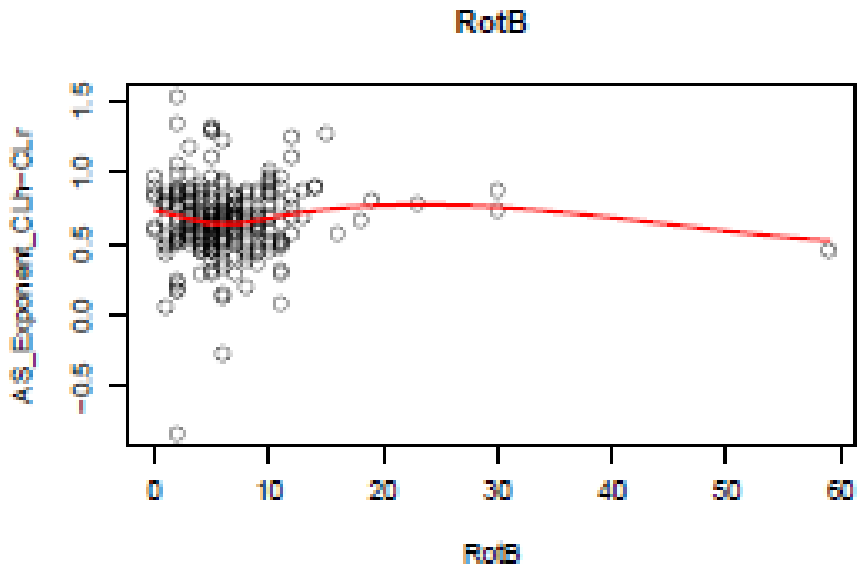
AS_Exponent_CLh-CLr
PSA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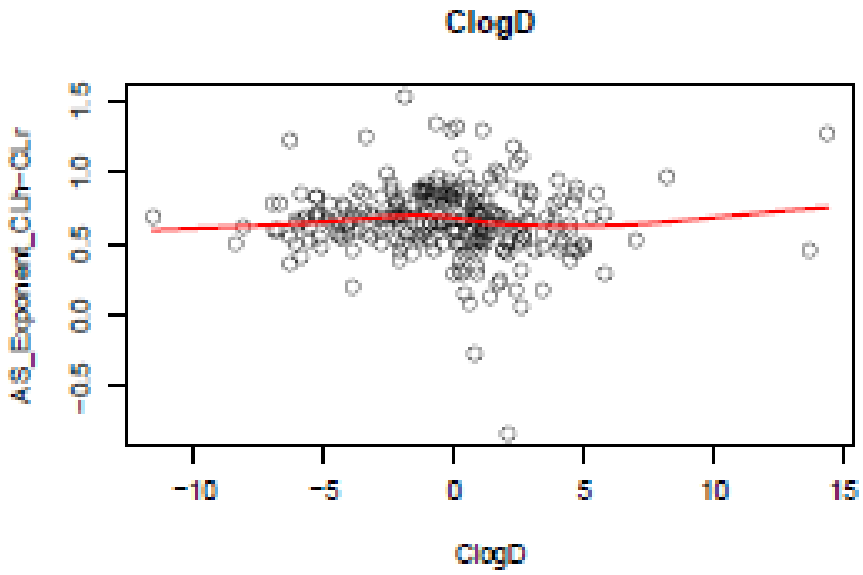
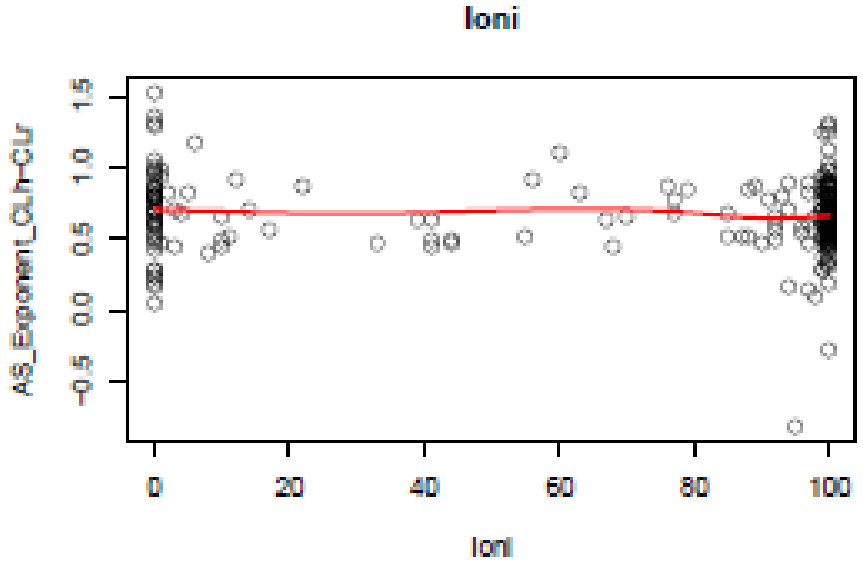
RotB


ClogD
AS_Experim_CLh~CLr
ClogD


Ioni
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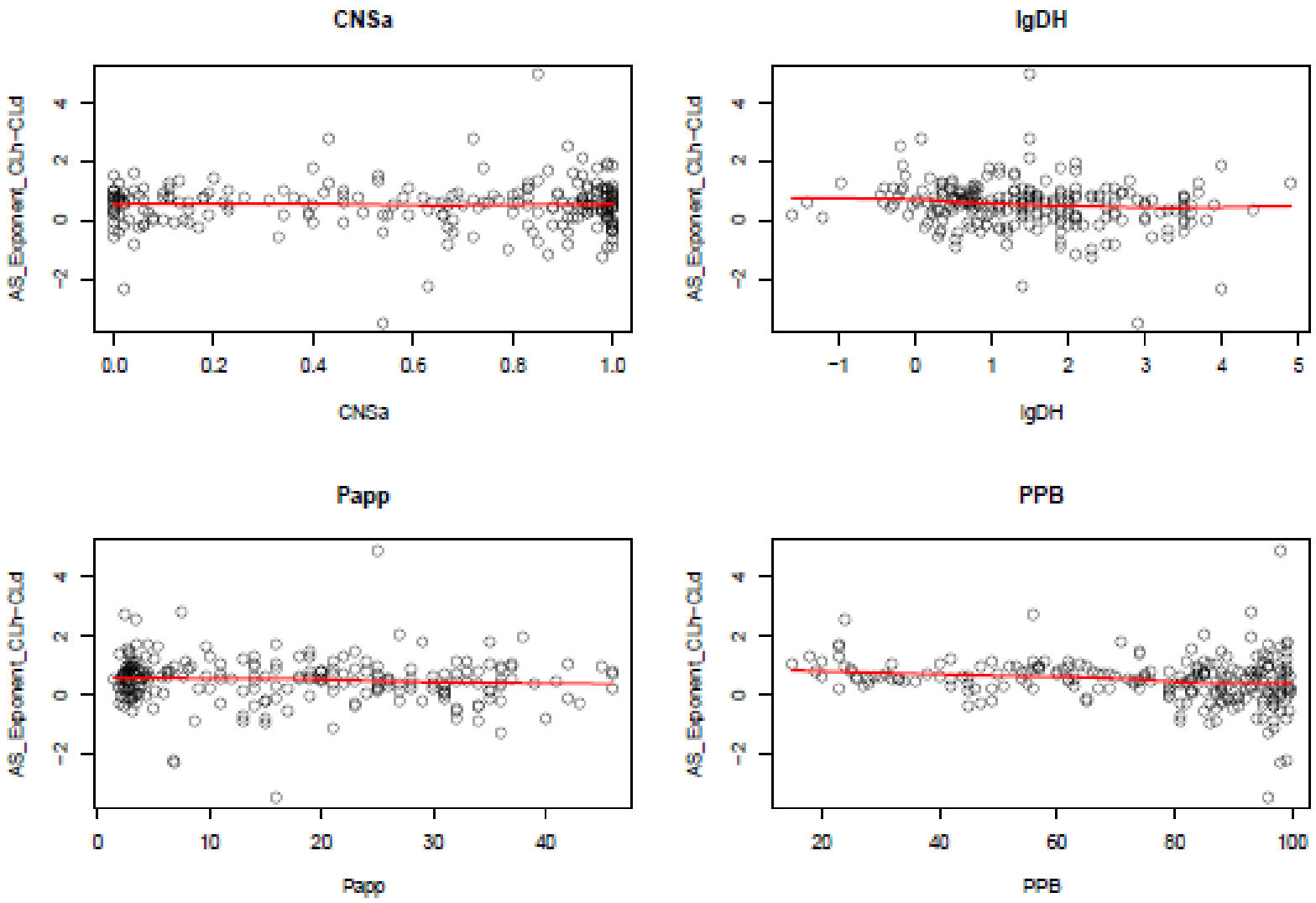
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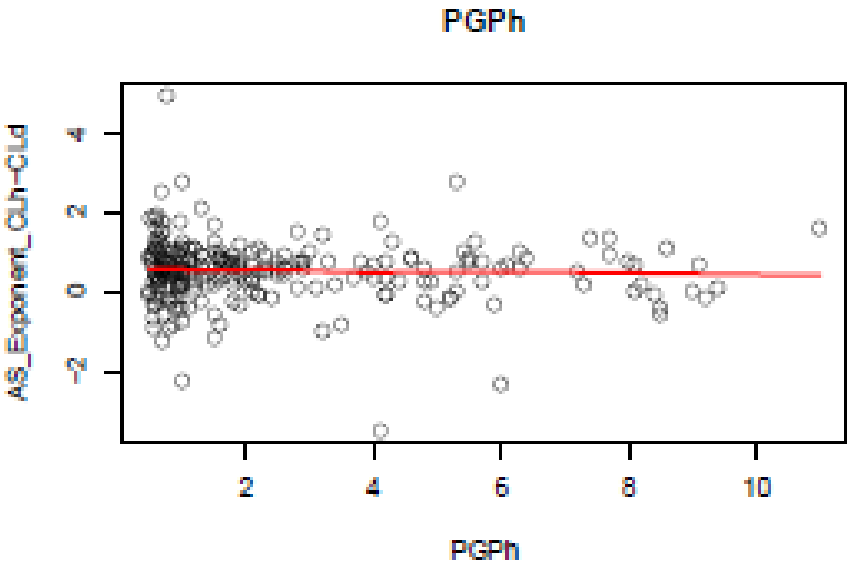
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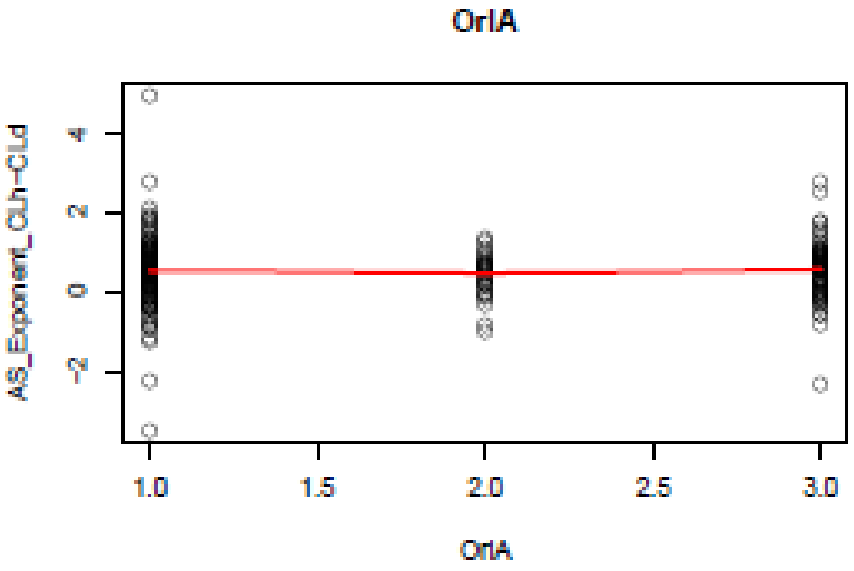
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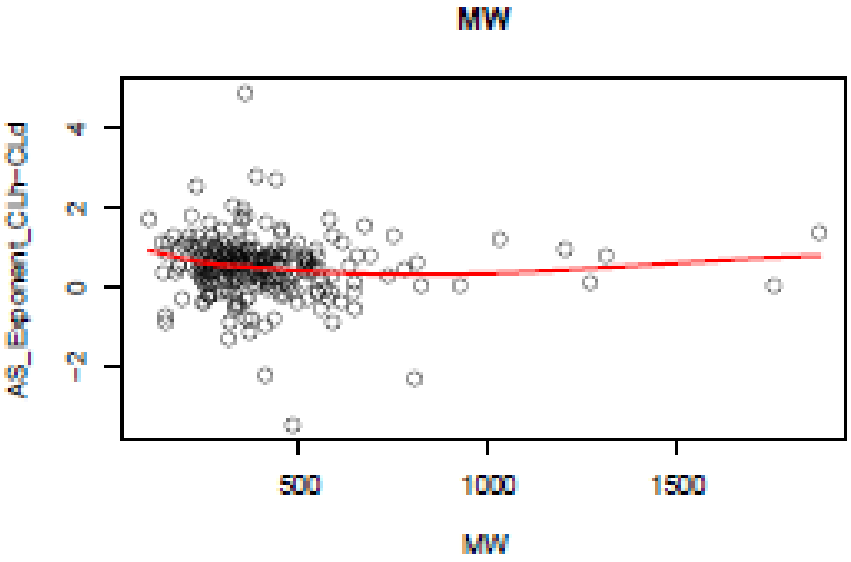
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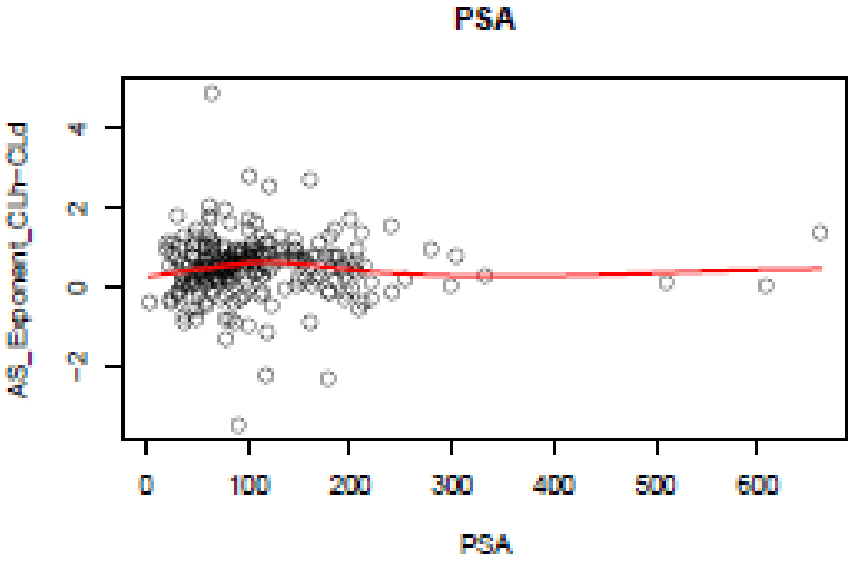
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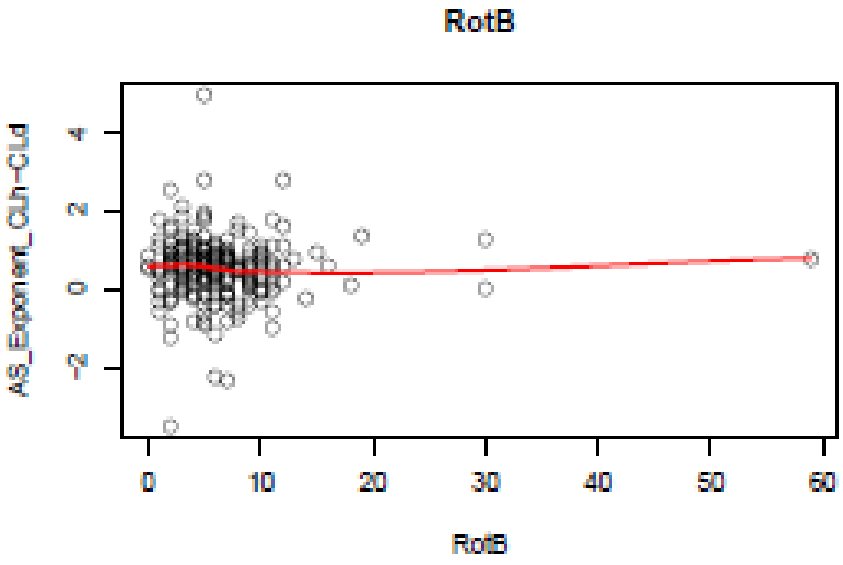
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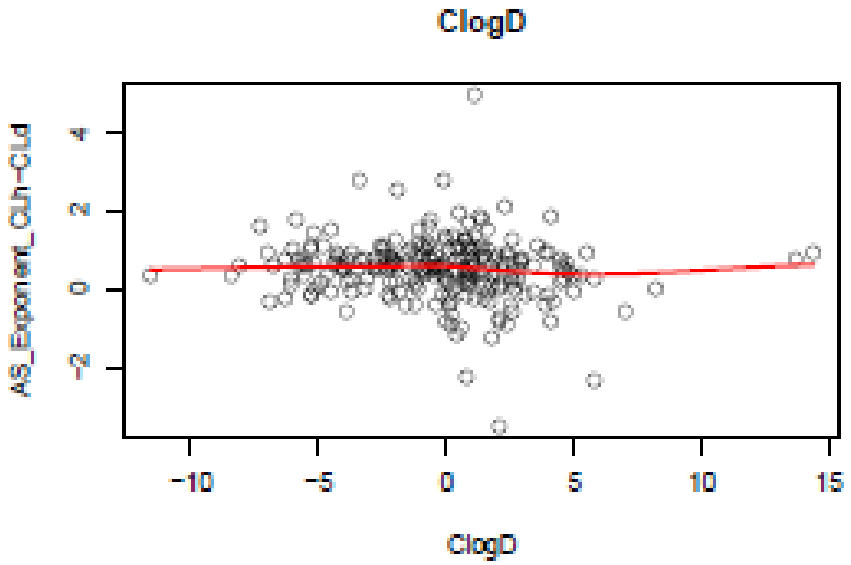
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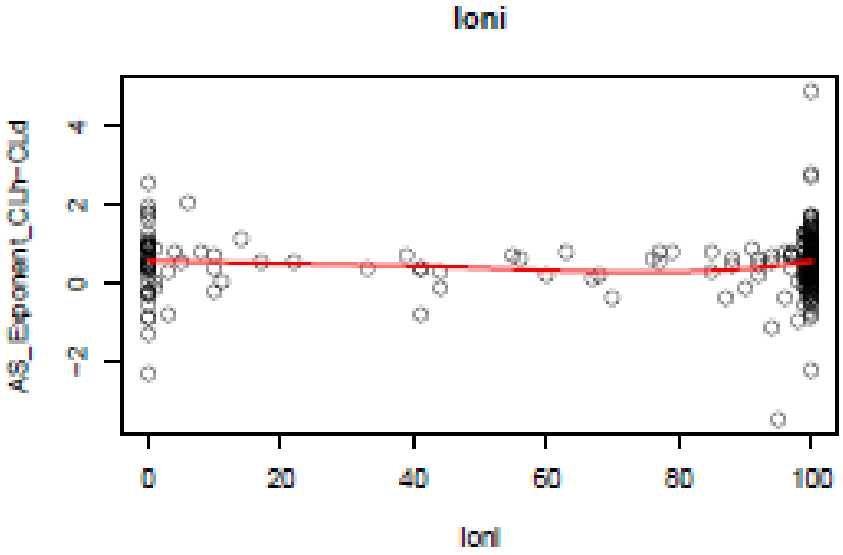
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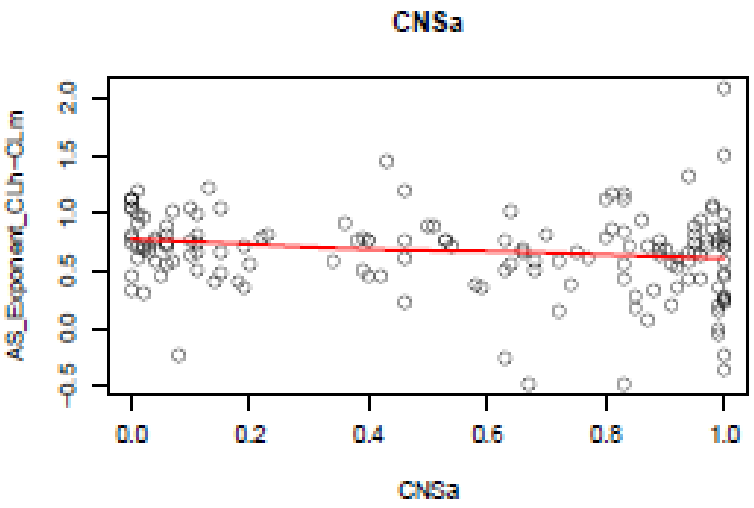
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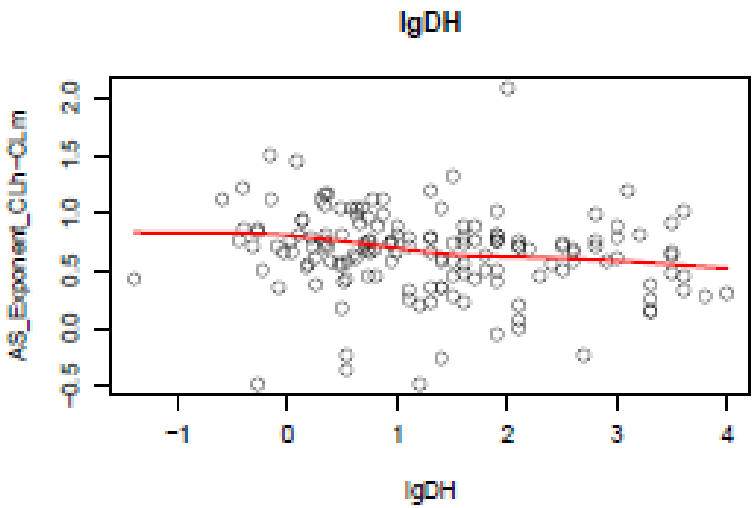
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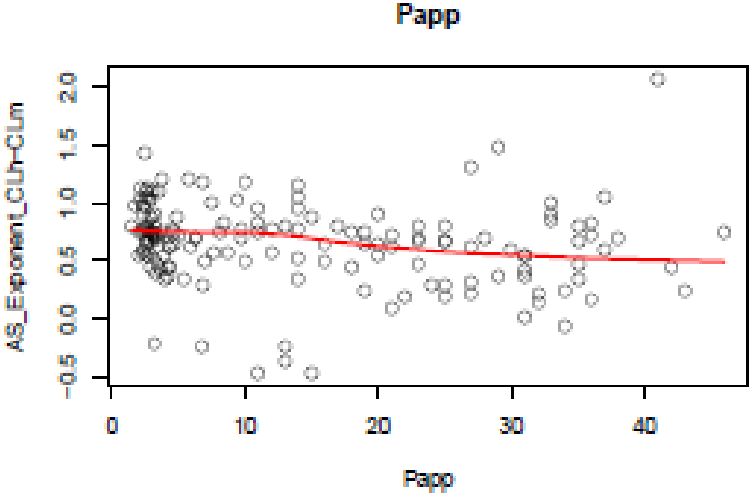
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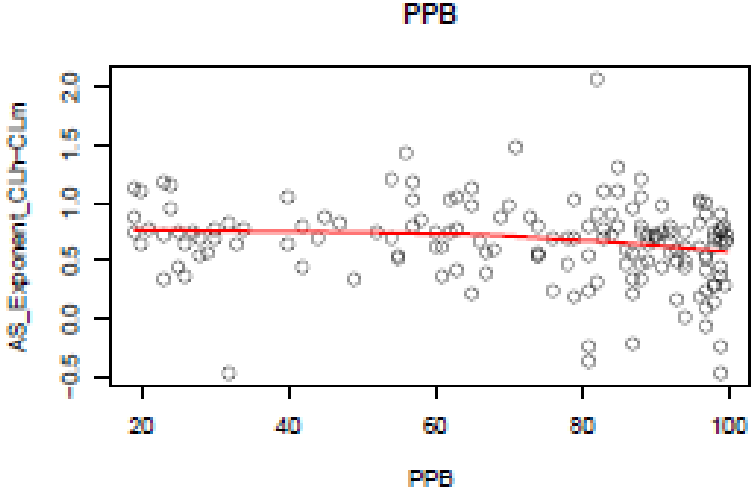
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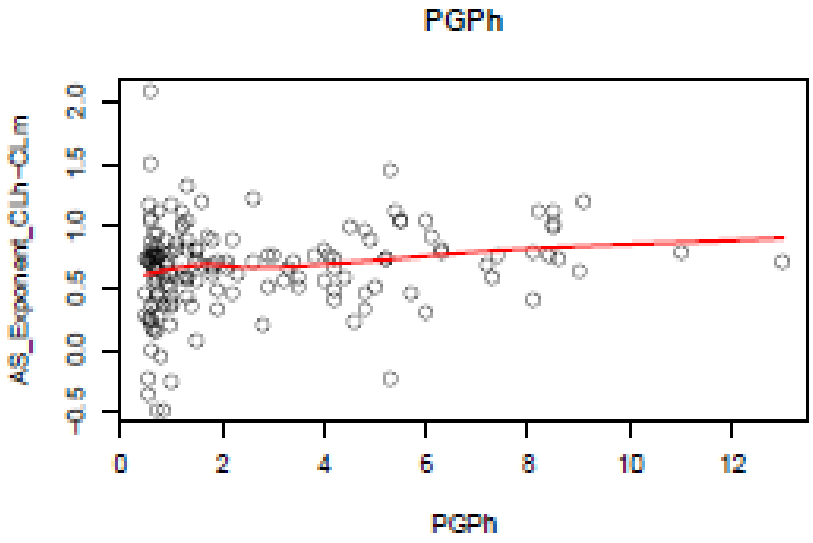
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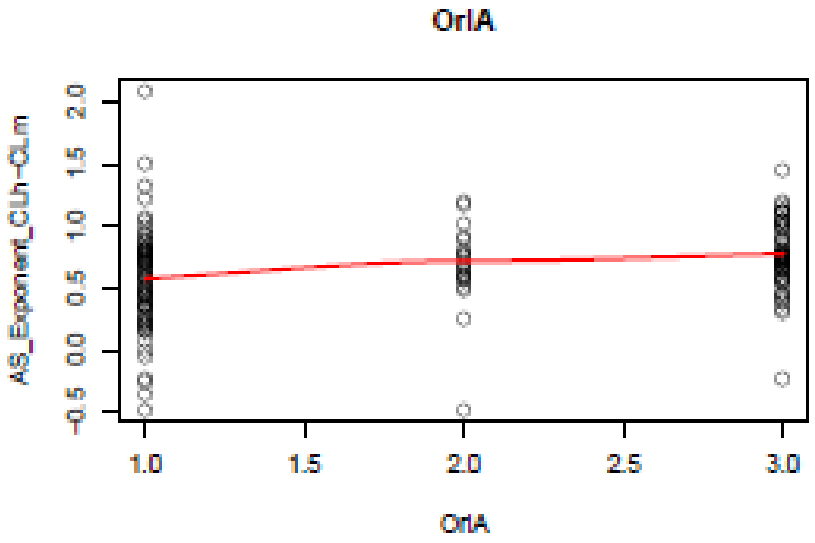
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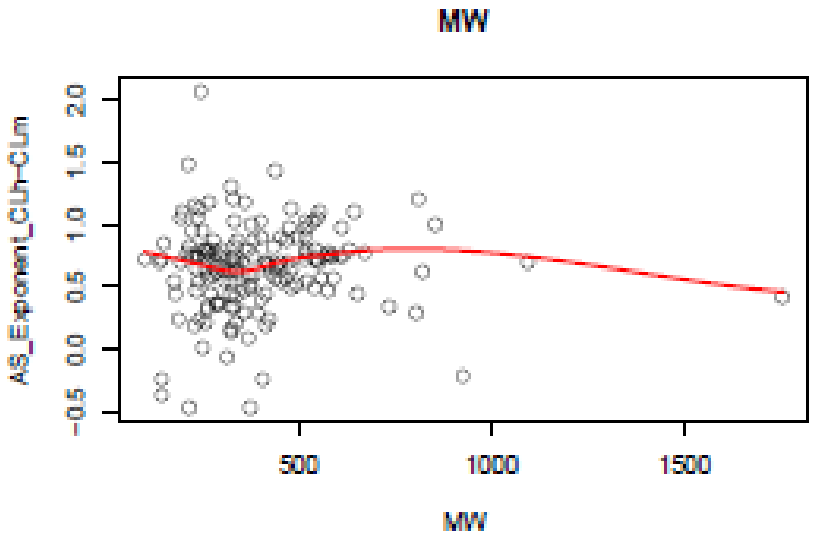
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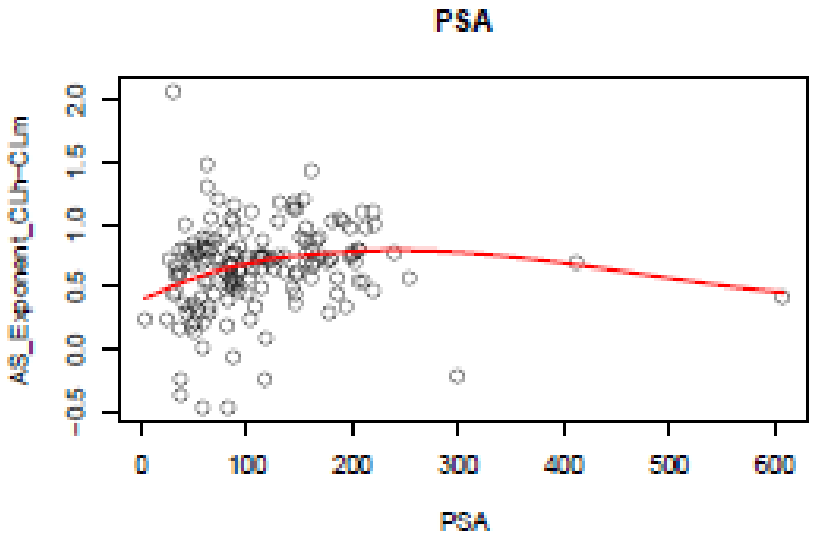
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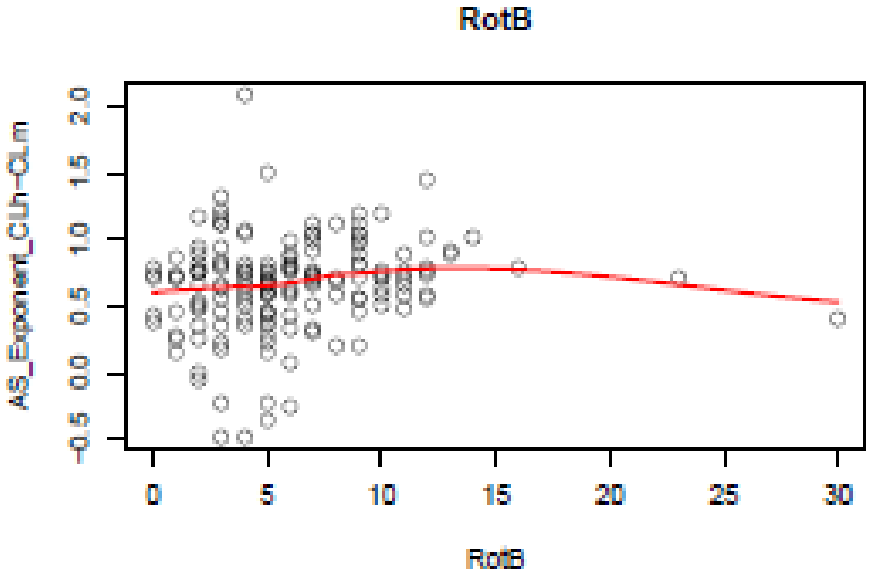
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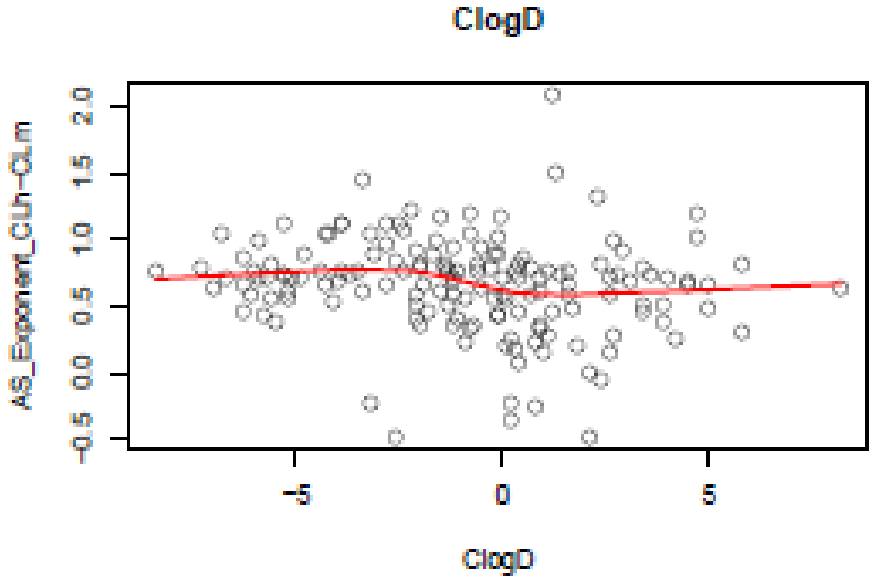
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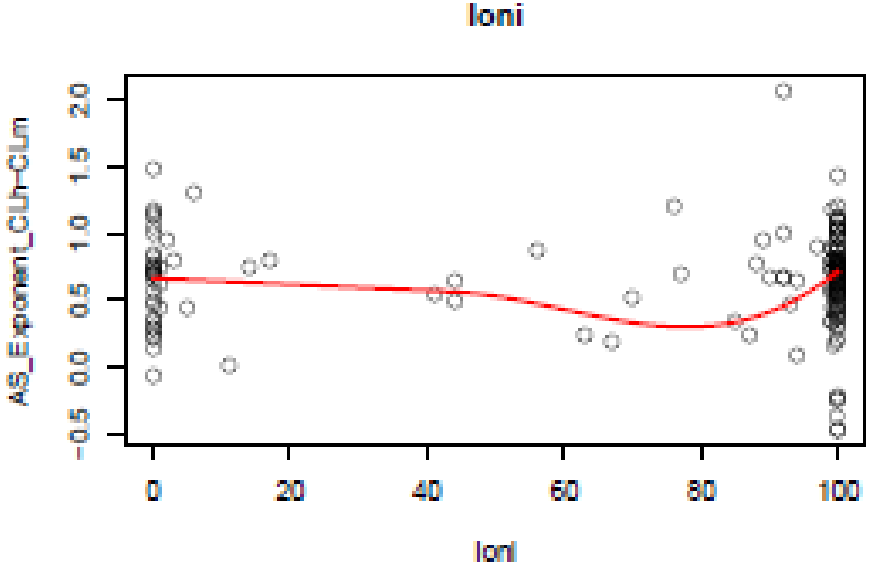
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CHAPTER 4

EVALUATION OF METHODS IN ANALYZING ALLOMETRIC POWER FUNCTIONS IN PREDICTING HUMAN PHARMACOKINETICS: A COMPARISON OF LOG-LOG TRANSFORMATION FOLLOWED BY LINEAR REGRESSION VERSUS DIRECT NONLINEAR REGRESSION

1_Abstract

Objective: Animal and human systemic clearance (CL) data were collected and used for evaluation and cross comparison of methodologies in allometric functions analysis, namely the log-log transformation followed by linear regression (LL-LR) and direct nonlinear regression (NLS) with different weighting schemes. Central tendency and distribution of the allometric exponents were evaluated and compared. More importantly, the human CL prediction performance was evaluated among the methods.

Methods: Pharmacokinetic data following intravenous administration for 251 drugs with CL in at least 3 species (including human) were used in this study. LL-LR and NLS functions with weighting functions of $1/CL^{1/2}$, $1/CL$, $1/CL^{3/2}$, $1/CL^{2}$, $1/CL^{3}$ and $1/CL^{4}$ were coded in R Software for analysis. Allometric exponents, statistics (including root mean square error (RMSE%), BIAS%

and R^2), and the prediction performance (individual predicted/observed, absolute average fold-error (AAFE), average fold-error (AFE), ranges, etc.) were evaluated across different methods.

Results: The LL-LR method and the NLS with $1/CL^2$ weighting resulted in the most similar allometric exponent with central tendency around 0.668. This value is close to what has been reported in literature. In addition, these two methods provided the best predictability among the different methods, which supports the widely used LL-LR method used for pharmacokinetic interspecies scaling. Furthermore, the statistic indices, R^2, RMSE% and BIAS%, were all shown to bear poor correlations with the prediction performance. Lastly, LL-LR analysis corrected by MLP and BrW were demonstrated to be no better, or even worse, than the direct LL-LR method.

2_Introduction

Allometric scaling (AS) is grounded on the similarity of anatomical, physiological and biochemical variables in mammals (1)(2). The application of allometry was introduced into the biology field by Sir Julian Huxley in his 1932 book entitled *Problems of Relative Growth*, which defined the concept of "size and its consequence"(3). Basal metabolic rate (BMR) with body size is one of the most investigated AS relationships in comparative biology. AS being introduced from comparative biology by Dedrick in 1970s has been widely used in pharmacokinetics (PK) for the prediction of human PK parameters, including drug clearance (CL) based on *in vivo* animal data (2)(4). The AS relationship can be expressed mathematically by the power function $PK = a\ (W)^b$, where PK, in this case, is CL, W is species body weight, a is the allometric coefficient and b is the allometric exponent.

In the traditional comparative biology and pharmacokinetic method of analysis, the log transformation of both sides of the AS power function [Log(PK) = Log(a) + b Log(W)] is followed by linear regression (LL-LR) to obtain the allometric exponent and coefficient (5)(6). However, there has been little evidence to demonstrate that the LL-LR method is the most optimal for solving the power law function to predict human PK. As one of the principal techniques used in predicting human PK from animal data, AS has played an important role in drug discovery. Failure in predicting human PK would substantially impact drug development (7).

LL-LR: History of Applications in Comparative Biology and Pharmacokinetics

One of the major reasons that LL-LR has been historically popular is its easy usage. This was particularly true and important in the era when computers were not available. The LL-LR

method could virtually be done manually. The first step is to linearize the nonlinear data by log-transformation of X and Y data. The second step, linear regression, could be done graphically. The analytical solutions of the coefficient and exponent can also be derived from the minimization of least-squares. This method was widely used in comparative biology, of which the allometric analysis of the basal metabolic rate (BMR) versus body weight was the most famous and extensively investigated (8). By LL-LR analysis, the well-accepted ¾ power law was developed, which states that the animal's metabolic rate scales to the ¾ power of the animal weight (8, 3, 9). In 1949, Adolph et al. analyzed the physiological parameters, such as blood flow, liver weight, and others, versus body weight across animal species, using the LL-LR method and concluded that those physiological parameters followed the allometric model as well (10). Dedrick first introduced the allometric scaling of PK parameters for drugs (2). Shortly after, Boxenbaum extensively expanded the concepts of allometric scaling introducing pharmacokinetic time, maximum life span potential (MLP) and brain weight (BrW) correction (11, 12, 14). Following the seminal works of Dedrick and Boxenbaum, reports of allometric scaling of PK parameters, have escalated. Later, a variety of derivatives of allometric methods were proposed and used, such as "rule of exponents"(13), correction of *in vitro* clearance and(14) correction of protein binding (15). Nevertheless, all these methods use the LL-LR analysis method.

LL-LR: Statistical Fundamentals

LL-LR analysis of the AS power function basically assumes the model with a multiplicative error as in Eq. (1),

$$CL = a \times W^b \times \exp(\varepsilon) \qquad (1)$$

where CL is the drug clearance and W is the body weight of the corresponding species, a is the allometric coefficient, and b is the allometric exponent and ε is the inter-drug variability. By taking the log of both sides of the equation, a linear model with additive error is derived, based on which a linear regression of log(CL) versus log(W) could be performed as shown in Eq.(2):

$$\log(CL) = \log(a) + b \times \log(\mathrm{W}) + \varepsilon \qquad (2)$$

Therefore, LL-LR is built upon the following principal assumptions: linearity of the relationship between the dependent variable, Log(CL), and the independent variable Log(W); independence of the errors meaning there is no serial correlation; homoscedasticity of the errors, which presents constant variance of the errors; and normality of the error distribution. Violation of any of these assumptions will cause a regression model to be biased or misleading (16).

Data transformation is often applied in statistical analysis. Validation of the assumptions on the original data distribution has become a normal practice before data transformation is employed in statistical analysis. In allometric analysis, however, this has been often neglected or not feasible, due, in part, to scarcity of the data. Typically PK parameters from only three or four species are employed. The regular assumption testing, such as constant variance and normality test of residuals, was often not feasible. Another limitaton of LL-LR is that log transformation compresses the data distribution in an unbalanced way. The high end of the distribution is affected more than the low end. The straight line fitted to the transformed data will exaggerate the influence of small values of the response variable. The small changes in slope may translate into large changes in estimates in the original scale (17-19).

In PK, Tang and Mayersohn derived a mathematical equation of LL-LR, which clearly shows that the contribution of PK parameters to the human prediction is different among animal species,

and the differences are largely determined by the animal body weight rather than the measured PK parameters in different species. This presents another defect in using LL-LR in analyzing the allometric power function (20).

In comparative biology, there have been a few limited reports, which challenged the use of LL-LR in analyzing allometric relationships, mainly focusing on the basal metabolic rate versus body weight. For example, the ¾ law has been challenged in a statistical perspective that the ¾ exponent could not be statistically differentiated from an exponent of 2/3 (8, 21, 22, 9). Others also reported that the exponent of basal metabolic rate could be different from that based on LL-LR if different methods are used for analysis of power function (23).

Another important note to the LL-LR method is that the coefficient of determination (R^2) is an insufficient or inappropriate statistical index in assessing the correlations of nonlinear models (24, 25). Often high R^2 in allometric analysis has been used to claim excellent correlation and high confidence in prediction. It has been shown, however, that the R^2 is theoretically expected to be high for LL-LR with typical allometric PK data as W and CL typically covers more than a 100-fold range. Further, there is weak correlation between prediction performance and R^2 (25).

In summary, the allometric relationship is largely empirical and the LL-LR method is associated with assumptions that cannot be statistically validated. However, the ready availability of computers allows for direct nonlinear regression. In this study the performance of the direct nonlinear regression methods encompassing different weighting functions was compared to the LL-LR method in analyzing the AS power function, including their accuracy and precision on human CL prediction. The simple direct LL-LR method was also compared with the MLP and BrW corrected LL-LR methods.

3_ Methods

Data Set

Pharmacokinetic data following intravenous administration for 251 drugs with CL in at least 3 species, including humans, found in the literature were used as the main data set in this study. This main data set (n = 251) was then used as the data set for the first analysis in this study to retrospectively evaluate AS exponents. Out of the main data set, the compounds with CL data from 3 animal species, excluding humans, were extracted and used as the data set (n = 133) for the second analysis in this study to conduct human CL prediction comparison across methods. This data set was also used for the third analysis in this study to evaluate three statistical indices for prediction performance.

Data Analysis Strategy

Two major methods were used to estimate the AS parameters. The first method of analysis employs linear regression analysis of log transformed data. The second method used a weighted nonlinear regression by minimizing the objective function through an iteration process judged by the Gauss-Newton optimization algorithm.

The methodology in this study included three different analyses. The first analysis compared NLS and LL-LR on each drug in the main data set, which includes human CLs, to retrospectively estimate the distribution and central tendency of the AS exponent by different methods and weightings. In the second analysis, NLS and LL-LR were performed on each compound in the data set which did not include human CL values, to obtain the AS exponents. Based on these results, the predicted human CL for each compound was calculated and compared with the observed human CLs. The goal of the second analysis was to determine the accuracy and

precision of human CL prediction across different approaches. The third analysis was to evaluate correlation of the commonly used statistical indices R^2, RMSE and bias versus human CL prediction performance. Poor description of coefficient of determination using R^2 for a nonlinear model has been well recognized (26) The relative root mean squared error (RMSE), which is used to describe precision and the mean prediction error (bias), was considered to provide better description of predictive performance (26). The RMSE% and bias% for direct nonlinear regression method with different weightings and LL-LR were calculated. These RMSE and bias values were evaluated against the human CL prediction performance, with the attempt to assess the appropriateness of using RMSE and bias as the statistical index, rather than R^2.

LL-LR

The AS approach of LL-LR was performed for each compound in the data sets with human CLs and the data set without human CL values). After taking the logarithm of both sides of the nonlinear AS power equation: $\log(CL) = \log(a) + b \times \log(W)$, a linear regression function was applied to obtain parameter estimates log(a) and b using software R. This operation was based on the assumption that log-transformed inter-drug variability is additive and follows a normal distribution.

As for the comparison investigation on MLP and BrW corrected LL-LR, from the MLP and BrW corrected AS method original paper, the MLP of 5.24, 18.4 and 22.9 years, and BrW of 2.48, 63.7 and 66.0 grams, for rat, dog and monkey, respectively, were introduced to the log transformed CL values. Linear regression was thereafter conducted on the MLP or BrW corrected CLs to get human CL prediction (CL/MLP or CL/BrW). A median human MLP of 93.5 years and BrW of 1533 grams were then used to calculate the predicted human CLs (11).

Nonlinear Regression

The NLS with different weightings were directly performed by fitting the allometric equation to each compound in both data sets. The Gauss-Newton algorithm was applied for optimizing the objective function values. The weights were set as the reciprocal of CL raised to various powers: $1/CL^{1/2}$, $1/CL$, $1/CL^{3/2}$, $1/CL^{2}$, $1/CL^{3}$, $1/CL^{4}$. Initial values of the coefficient and exponents were set at 10 and 0.6, respectively. For each weighting, there were a few compounds for which NLS could not succeed in minimization with the standard set of initial values. A manual adjustment of initial values of either coefficient and/or exponent was introduced. This adjustment was conducted repeatedly until successful minimization was achieved.

Assessment of Prediction Performance

Absolute average fold-error (AAFE) was used to assess the precision of predictions (27) defined as, where n is the total number of compounds analyzed as in Eq. (3):

$$AAFE = 10^{\Sigma\left|\log\left(\frac{pred}{obs}\right)\right|/n} \qquad (3)$$

A smaller AAFE indicates a better prediction performance. For example, AAFE at 2 means an overall "averaged" prediction is 2-fold over or under the observed values.

Average fold-error (AFE) was used to assess the overall bias of prediction, defined as Eq. (4):

$$AFE = 10^{\Sigma\log\left(\frac{pred}{obs}\right)/n} \qquad (4)$$

An AFE value <=1, =1, and >1 means there is an overall under, no, and over-predictions relative to the observed values, respectively. In addition, the prediction performance was also assessed by the percentage of fold-error (Predicted human CL/Observed human CL) out of a

certain range, such as [-0.1, 10] and [0.3, 3]. These ranges represent the commonly used prediction percentage 10 and 3 folds, respectively.

The human CL prediction performance was also evaluated by the bias and root mean square error. Bias and the root mean square error (RMSE) were expressed as Eq. (5):

$$bias\ \% = \frac{\sum_i^n (Y_i - \hat{Y}_i)/n}{\sum_i^n \hat{Y}_i/n}$$

$$RMSE\ \% = \sqrt{\frac{\sum_i^n (Y_i - \hat{Y}_i)^2/(n-2)}{\sum_i^n \hat{Y}_i/n}} \qquad (5)$$

where n is the number of animal species for each compound.

R Software and Programming

The software R 2.8.1 was used for all analyses. The NLS function is used for estimating parameters via least squares. It assumes that the errors (ε) are independent with variance σ^2/w, where w is the known weighting and σ^2 is the unknown variance to be estimated. Different weighting schemes as described above were used with NLS. Unlike linear regression, where the parameter estimates can be solved analytically, nonlinear regression by minimization of least-squares doesn't offer an analytical solution. Rather, NLS uses an iterative procedure, which searches for the minimizer of the least-square via an algorithm. A Gauss-Newton algorithm is the default with NLS. The programming codes for NLS are provided in **Appendix 1**. And, the example R code for the programming of RMSE%, BIAS% and R^2 are presented in **Appendix 2.**

4_Results and Discussion

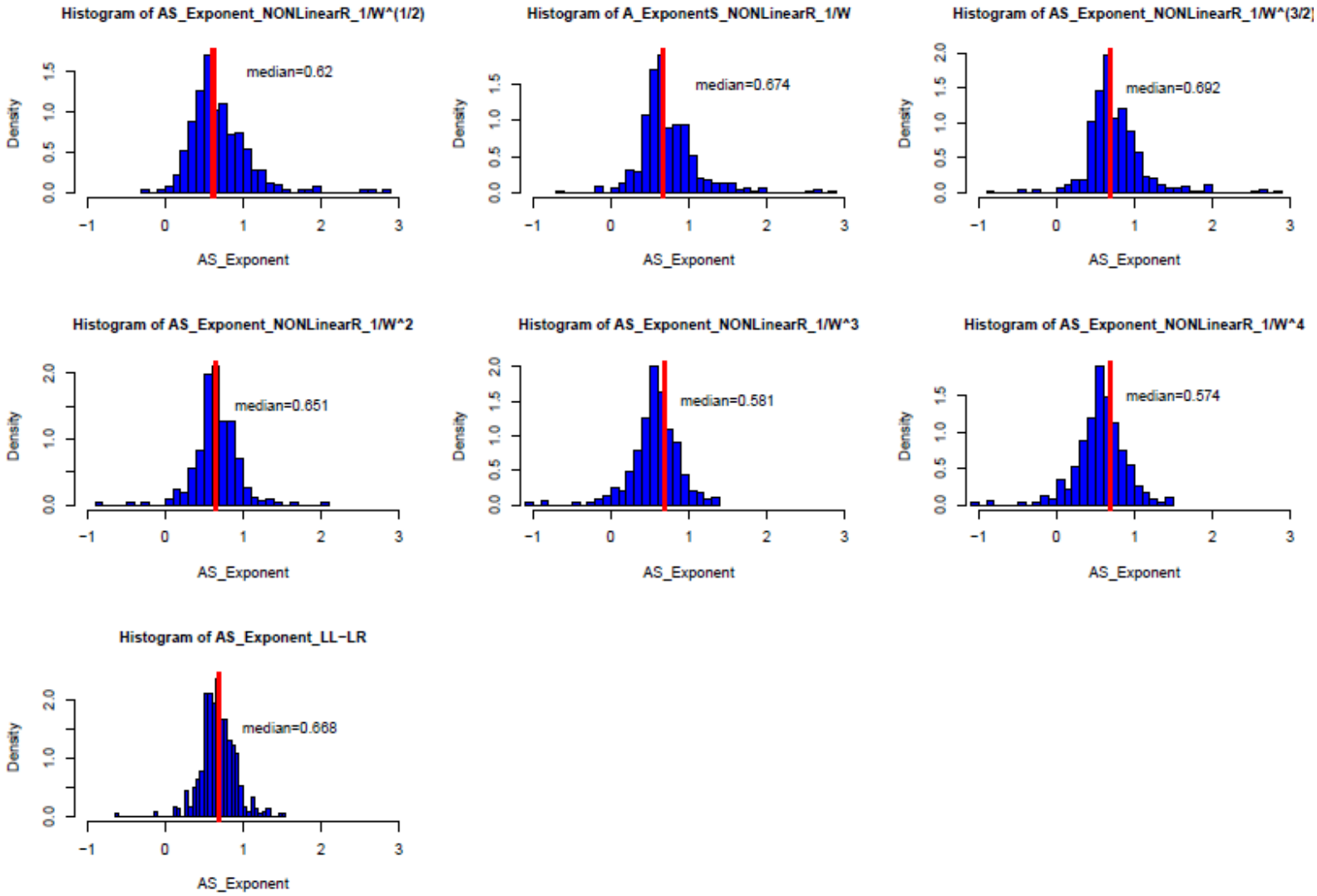
For the first analysis based on the data set that includes human CLs, the estimated AS exponent distributions and central tendencies estimated from NLS with different weightings and LL-LR are presented in **Figure 1** and **Table 1.** The estimated AS exponent distributions through NLS with different weightings versus LL-LR are generally consistent. Among them, the AS exponent distribution estimated from NLS with weighting of $1/CL^2$, $1/CL^1$, $1/CL^{1.5}$ demonstrate similar distributions compared to LL-LR. As for the comparison of AS exponent central tendencies, the estimated AS exponent median value of 0.674 through NLS with weighting 1/CL is most similar to that of LL-LR (0.668). At the same time, the other NLS with weightings $1/CL^2$ and $1/CL^{1.5}$ also provided AS exponent estimations of 0.651 and 0.692, respectively, within the ±5% difference from LL-LR. For the weighting $1/CL^{0.5}$, $1/CL^3$ and $1/CL^4$, there were relatively bigger differences compared to results from LL-LR estimation. These results demonstrated that through the approaches of LL-LR and NLS with weighting schemes of $1/CL^2$, $1/CL^1$, $1/CL^{1.5}$ to perform AS could lead to similar AS exponent estimations and further similar human CL predictions. Given there are substantial outliers at the high end for NLS with weighting schemes of $1/CL^1$, $1/CL^{1.5}$, the NLS approach with weighting $1/CL^2$ was considered to be the most similar method to LL-LR.

It is worthwhile to mention that the AS exponent estimation results, both distribution and central tendency through NLS with weighting $1/CL^2$, $1/CL^1$, $1/CL^{1.5}$ as well as LL-LR are similar to what Hu et al. reported in 2001 (29). In conclusion, the results from our study based on this large diverse data set suggests the AS exponent values for CL around the exponent rule of 2/3 (0.668).

Table 1. Estimated AS exponent central tendencies and percent difference between NLS with weightings compared to LL-LR based on data set including humans

Weighting function	AS Exponent	% Difference Compared to LL-LR
$1/w^{0.5}$	0.620	-7.2
$1/w^{1}$	0.674	0.90
$1/w^{1.5}$	0.692	3.6
$1/w^{2}$	0.651	-2.6
$1/w^{3}$	0.581	-13
$1/w^{4}$	0.574	-14
LL-LR	0.668	---

Figure 1. Predicted AS exponent distributions and central tendencies based on NLS with different weightings and LL-LR based on data set that includes humans



For the second analysis based on the data set which does not includes human CL values, the human CL prediction performance was assessed by three types of statistical measures, namely, AAFE, AFE and percentage of fold-error out of ranges as shown in **Table 2** and **Figure 2.** The AFE and AAFE were estimated to be 0.74 and 2.92 by NLS with weighting $1/W^2$, which represents the closest estimation towards "1" for AFE and the smallest AAFE compared to other weightings. At the same time, the percentage of fold-errors out of ranges [0.1, 10] and [0.3, 3] for NLS with $1/W^2$ weighting method were calculated to be 7.52% and 31.6%, respectively, which illustrated the narrowest ranges compared to other NLS weightings tested. This trend could also be identified among plots (A) to (G) in **Figure 2.** There were less observed data points located outside of the 0.3 to 3 fold lines (green lines) in NLS with weighting $1/W^2$ plot (plot (B)) compared to other NLS weighting methods. By LL-LR method, the AFE and AAFE were estimated to be 1.38 and 2.63, respectively, and the fold-errors out of ranges [0.1, 10] and [0.3, 3] were estimated accordingly to be 8.27% and 28.6%. By inspecting plots in **Figure 2** there are even less observed CLs data scattered outside of the 0.3 to 3 fold lines from LL-LR method (plot(A)) compared to NLS with weighting $1/W^2$ (plot(B)). The overall statistics showed that the methods with performance were ranked by LL-LR and $1/w^2 > 1/w^3$ and $1/w^4 > 1/w^{1.5} > 1/w > 1/w^{0.5}$. The NLS with $1/W^2$ weighting and LL-LR were considered to demonstrate similar human CL prediction precision and accuracy in this study.

Between LL-LR and NLS with weighting $1/w^2$, the AFE (bias) was at 1.38 and 0.74, respectively, which suggested LL-LR generally over-predicts CL, while NLS (weighting $1/w^2$) under-predicts CL. Therefore, retrospectively, an additional empirical method was proposed. The proposed method is performing AS by LL-LR and the NLS with weighting $1/W^2$ separately. As a following step, for each compound in the data set, the predicted human CLs based on these two

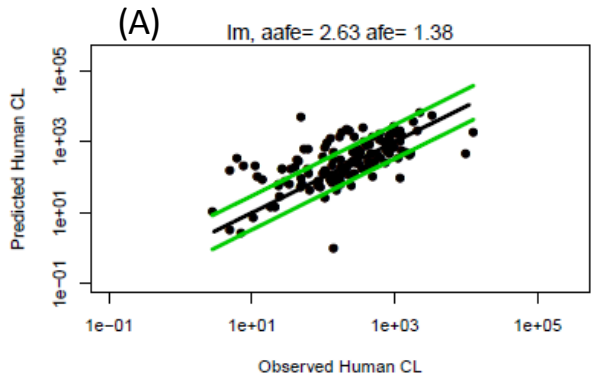
different approaches were averaged and the resulted value was defined to be the final predicted human CL. The results are shown as plot (H) in **Figure 2** and in the bottom row of **Table 2.** This new proposed approach demonstrated a relatively better AFE and AAFE at 1.14 and 2.59, respectively. Compared to all other methods conducted in this study, including LL-LR and NLS with weighting of $1/w^2$, this newly developed empirical approach further improved the precision and accuracy of human CL prediction.

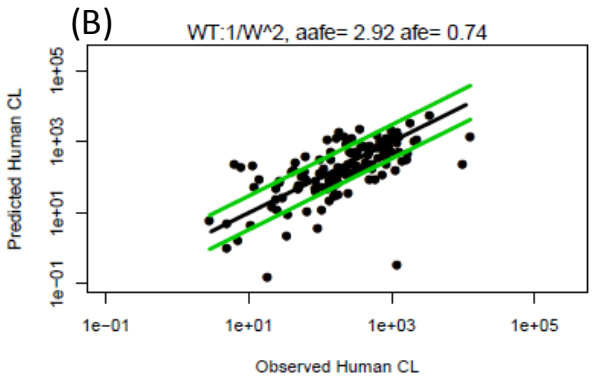
In summary, this work evaluated a wide range of NLS with weighting functions in analyzing the allometric function, and strongly confirmed that the application of the LL-LR is likely the best performing method, although the latter method is associated with many fundamental assumptions. At the same time, the current analysis suggests that the widely held assumption of log-normality of CL distribution in pharmacokinetic field is appropriate. In addition, a new empirical method, which averages the predictions between LL-LR and NLS weighted of $1/w^2$ appeared to improve the prediction. However, this method needs more rigorous external data to fully evaluate it.

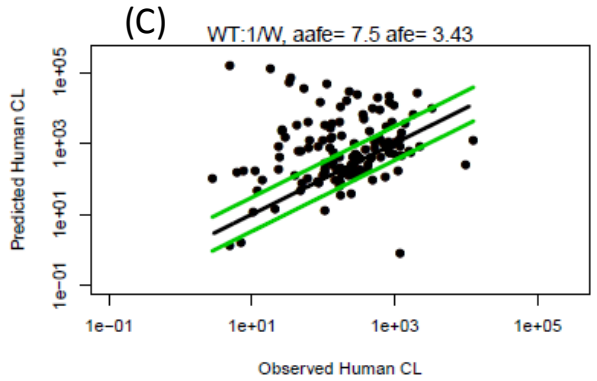
Table 2. Human CL prediction performance comparison among NLS and LL-LR: AAFE and AFE, percentage of fold-errors out of ranges [0.1, 10] and [0.3, 3]

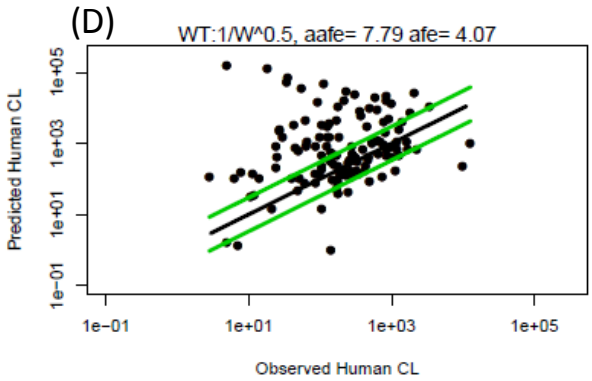
Weighting function	AFE	AAFE	% out of [0.3, 3]	% out of [0.1, 10]
$1/w^{0.5}$	4.07	7.79	51.1	35.3
$1/w^{1}$	3.43	7.50	51.1	35.3
$1/w^{1.5}$	1.67	4.65	44.4	23.3
$1/w^{2}$	0.74	2.92	31.6	7.52
$1/w^{3}$	0.64	3.05	33.8	7.52
$1/w^{4}$	0.61	3.12	36.8	8.27
LL-LR	1.38	2.63	28.6	8.27
Mean Prediction of LL-LR and $1/w^{2}$	1.14	2.59	30.1	6.77

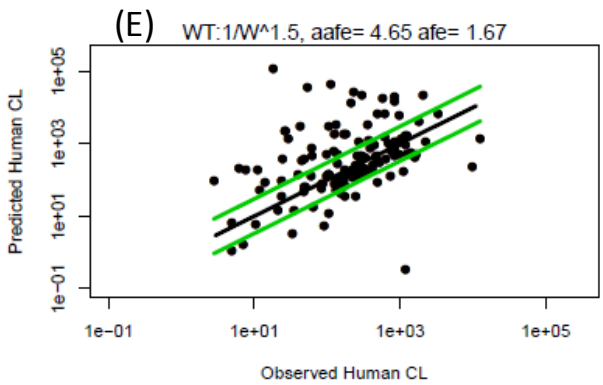
Figure 2. Observed versus predicted human CL values among different methods. The solid line represents the line of identity; The dashed lines indicate fold-errors at 0.3 and 3; and the black dots show observed CLs in different animal species for different compounds.

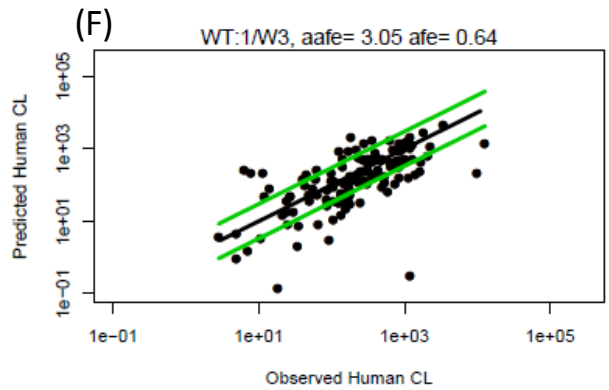

(A)
lm, aafe= 2.63 afe= 1.38
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05

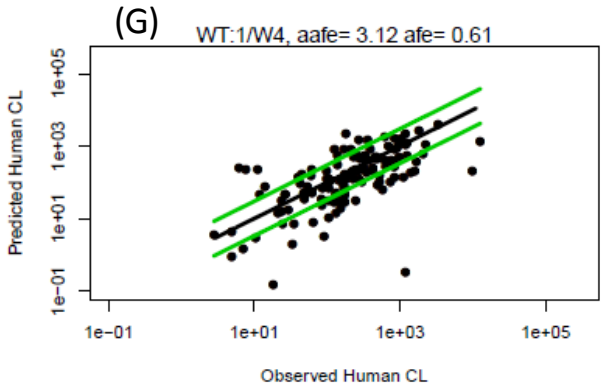

(B)
WT:1/W^2, aafe= 2.92 afe= 0.74
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05

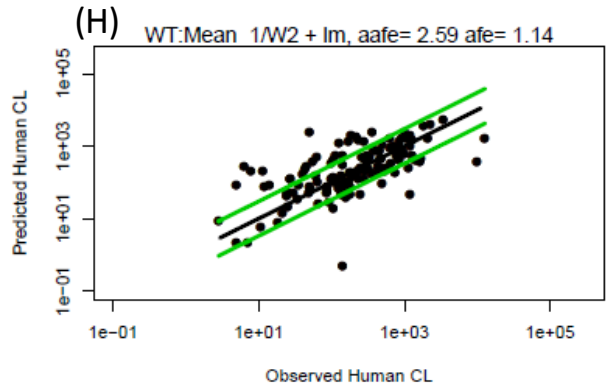

(C)
WT:1/W, aafe= 7.5 afe= 3.43
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05


(D)
WT:1/W^0.5, aafe= 7.79 afe= 4.07
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05


(E)
WT:1/W^1.5, aafe= 4.65 afe= 1.67
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05


(F)
WT:1/W3, aafe= 3.05 afe= 0.64
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05


(G)
WT:1/W4, aafe= 3.12 afe= 0.61
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05


(H)
WT:Mean 1/W2 + lm, aafe= 2.59 afe= 1.14
Predicted Human CL
Observed Human CL
1e−01
1e+01
1e+03
1e+05

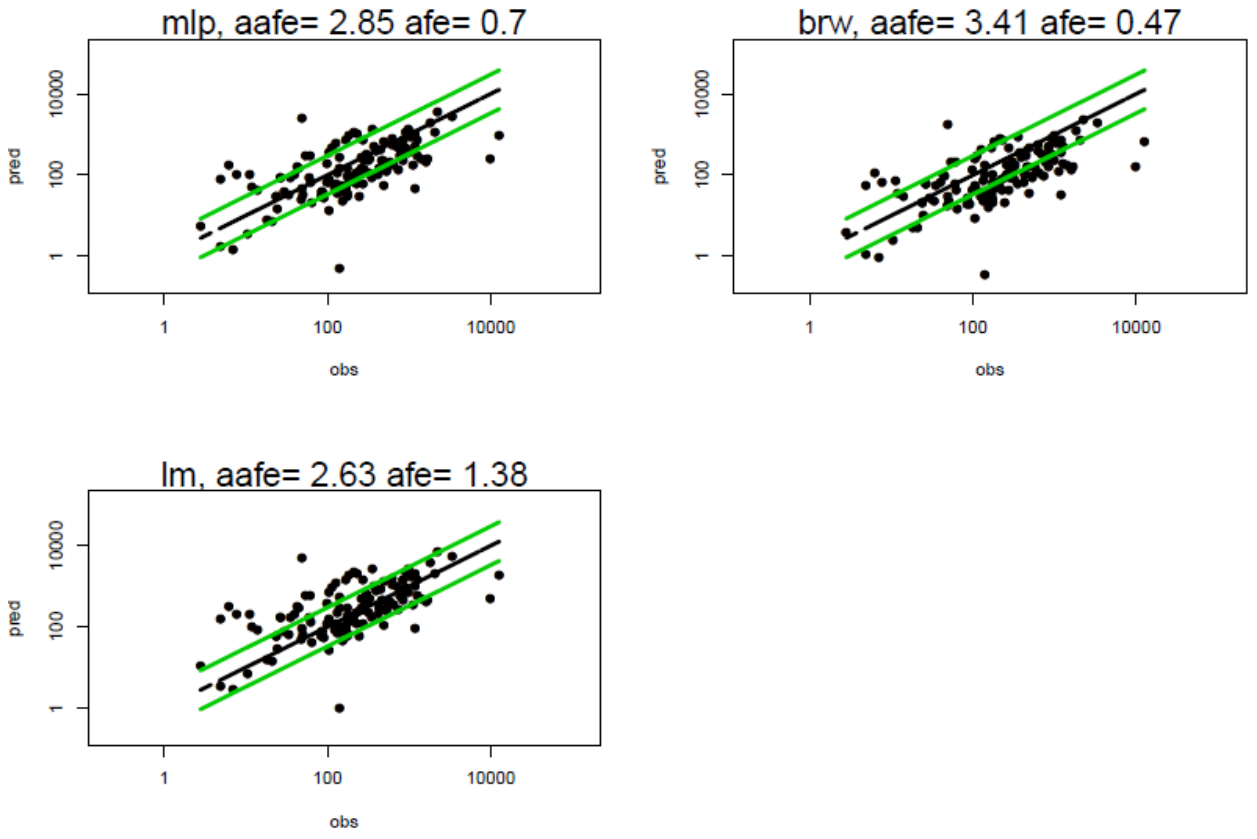
The predictions after MLP and BrW correction on LL-LR were compared to those without correction by LL-LR method demonstrated in **Table 3** and **Figure 3.** The AFE was estimated to be 0.7, 0.47 and 1.38 by MLP and BrW correction and direct simple LL-LR, respectively. These results confirmed that after MLP and BrW correction, all human CLs predictions were systemically downward shifted compared to direct LL-LR. The mathematical derivation by Tang and Mayersohn showed that there were 0.495 and 0.659 fold downward adjustment of the predictions by MLP and BrW correction, respectively, which was consistent with our finding in this study (28). This trend could also be identified in the plots in **Figure 3.** Compared to LL-LR method plot, the predicted data points were systemically downward shifted. The AAFE was estimated to be 2.85, 3.41 and 2.63 by MLP and BrW correction and the direct simple LL-LR, respectively. Apparently, precision was higher by the simple direct LL-LR approach. In addition, as pointed out by Tang and Mayersohn, such MLP and BrW adjustment were only dependent on the animal body weights among species and had no effect on the measured CL values.

Overall, the MLP corrected LL-LR appeared to perform similarly with simple LL-LR approach, while the BrW tended to over-correct the predictions. As shown in **Table 3.**, the percentage of fold-errors out of ranges [0.1, 10] and [0.3, 3] for direct LL-LR method were calculated to be 8.27% and 28.6%, respectively, which representing the narrowest ranges as compared to MLP and BrW correction approaches. In addition to the intrinsic defect pointed out by Tang and Mayersohn towards the MLP and BrW correction method, our analysis results in this study indicated that performing MLP and BrW correction on LL-LR did not provide better human CL prediction compared to direct simple LL-LR method.

Table 3. Comparison among MLP and BrW corrected LL-LR and simple LL-LR: AAFE and AFE, percentage of fold-errors out of ranges [0.1, 10] and [0.3, 3]

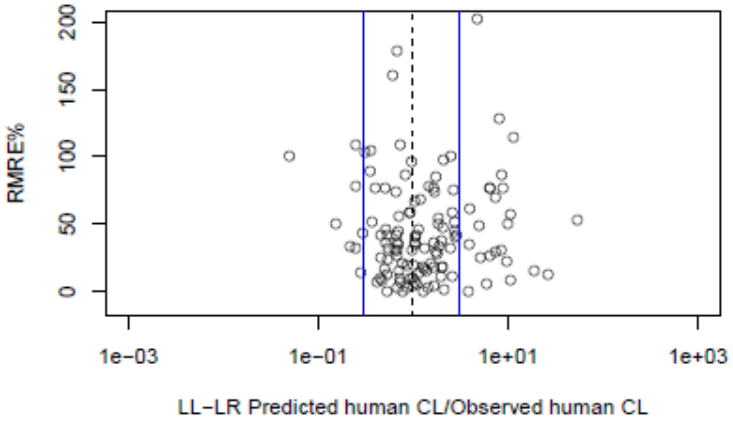
Methods	AFE	AAFE	% out of [0.3, 3]	% out of [0.1, 10]
MLP correction	0.70	2.85	37.6	6.02
BrW correction	0.47	3.41	46.6	9.02
LL-LR	1.38	2.63	28.6	8.27

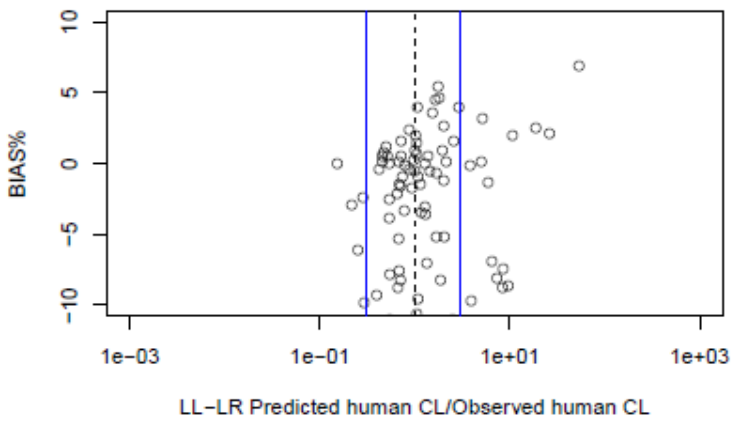
Figure 3. Predicted versus observed human CLs among different prediction methods: LL-LR corrected by MLP, LL-LR corrected by BrW as well as LL-LR. The solid line represents the line of Identity; The green lines indicates fold-errors at 0.3 and 3; and the black dots illustrate observed CLs in different animal species for different compounds.



Based results from the second analysis, the approaches of LL-LR and NLS with weighting of $1/W^2$ performed better for human CL prediction than other methods tested in this study. Therefore, the prediction performance versus statistics, including RMSE%, BIAS% and R^2, was evaluated on the LL-LR method. The evaluation results, predicted human CL over observed human CL ratio versus each of the statistic indices, are illustrated in **Figures 4 and 5.** Overall, none of the three statistic indices showed good correlations with the prediction performance. A poor correlation between R^2 and the prediction performance has been documented by other investigators (24)(25). The current analysis with a larger data size further confirmed the conclusion that application of R^2 in guiding the allometric prediction is not appropriate. The lack of correlation between RMSE% / BIAS% and prediction was demonstrated in allometric analysis for the first time with a large data set of experimentally obtained clearance values in different animal species. These results further show the difficulty in assessing the allometric relationship and thus predicting human values with limited species numbers. From a statistical point of view, this makes sense as well, since any model for statistical analysis with a sample size at 3 or 4 may be under-powered. Therefore, the statistic index R^2, RMSE% and BIAS% are not recommended to guide prediction performance in AS.

Figure 4. Comparison of R2, RMSE%, BIAS% versus prediction fold-error (three plots) for the LL-LR method. The black dashed line represents the prediction ratio = 1; the blue lines represents the prediction ratio at 0.3 and 3 fold.





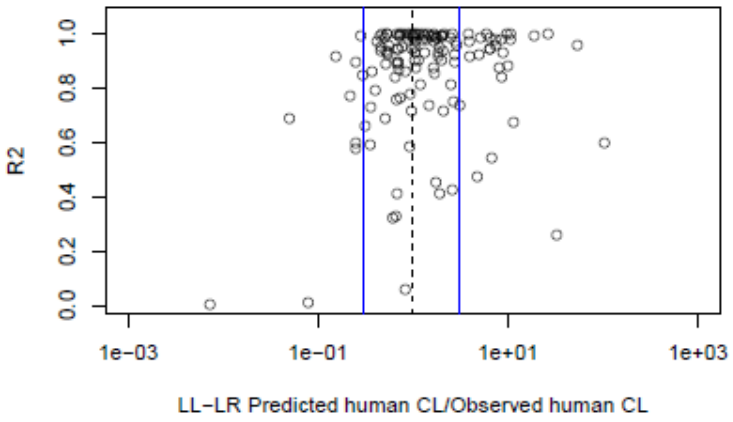
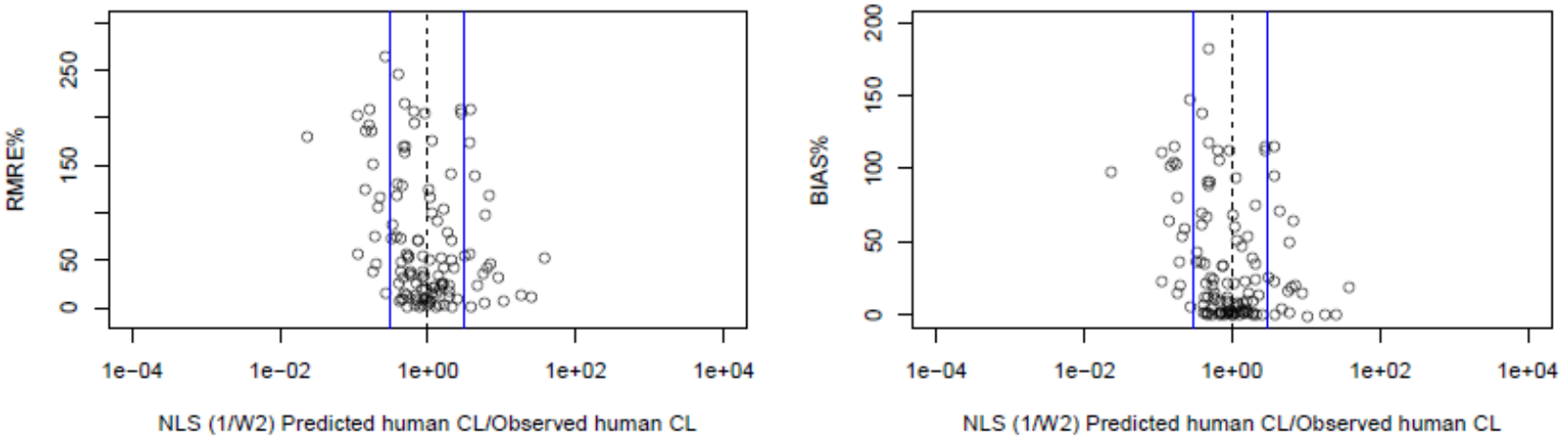


Figure 5. Comparison of RMSE%, BIAS% versus prediction fold-error (three plots) for the NLS weighted of $1/w^2$. The black dashed line represents the prediction ratio = 1 and the blue lines represent the prediction ratio at 0.3 and 3 fold.



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Appendix 1: Example R codes for NLS and weighting

Weight function:

```
wfct <- function(expr)
{
expr <- deparse(substitute(expr))
 ## create new environment
newEnv <- new.env()
  ## get call
mc <- sys.calls()[[1]]
mcL <- as.list(mc)
 ## get data and write to newEnv
DATA <- mcL[["data"]]
DATA <- eval(DATA)
DATA <- as.list(DATA)
NAMES <- names(DATA)
for (i in 1:length(DATA)) assign(NAMES[i], DATA[[i]], envir = newEnv)
 ## get parameter, response and predictor names
formula <- as.formula(mcL[[2]])
VARS <- all.vars(formula)
RESP <- VARS[1]
RHS <- VARS[-1]
PRED <- match(RHS, names(DATA))
PRED <- names(DATA)[na.omit(PRED)]
 ## calculate variances for response values if "error" is in expression ## and write to newEnv
if (length(grep("error", expr)) > 0) {
y <- DATA[[RESP]]
```

```
x <- DATA[[PRED]] ## test for replication
if (!any(duplicated(x))) stop("No replicates available to calculate error from!") ## calculate error
error <- tapply(y, x, function(e) var(e, na.rm = TRUE))
error <- as.numeric(sqrt(error)) ## convert to original repititions
error <- rep(error, as.numeric(table(x)))
assign("error", error, envir = newEnv)
} ## calculate fitted or residual values if "fitted"/"resid" is in expression and write to newEnv
if (length(grep("fitted", expr)) > 0 || length(grep("resid", expr)) > 0) {
mc2 <- mc
mc2$weights <- NULL
MODEL <- eval(mc2)
fitted <- fitted(MODEL)
resid <- residuals(MODEL)
assign("fitted", fitted, newEnv)
assign("resid", resid, newEnv)
} ## return evaluation in newEnv: vector of weights
OUT <- eval(parse(text = expr), envir = newEnv)
return(OUT)
}
```

nls function:

```
myNls <- nls(cl~ coefficient * wt^slope, data = temp,
start = c(coefficient = iniCOE[i], slope = iniSLP[i]), weights = wfct(1/cl^2))
```

Note: Where iniCOE and iniSLP are the initial supplied values for the coefficients and exponents, respectively; wfct is the weighting function (CL^2 in this example).

Appendix 2: Example R codes for the programming of RMSE%, BIAS% and R^2

```
myAllom <- read.csv("…\\AS_pros_III\\wo_huamn_AS\\data2.csv")
myAllom2 <- read.csv("…\\AS_pros_III\\wo_huamn_AS\\myini-woH-WT1.csv")

myAllom <- myAllom[myAllom$mdv!=1,]
mode(myAllom)
myAllom$cl <- as.numeric(as.character(myAllom$cl))
myAllom$wt <- as.numeric(as.character(myAllom$wt))
ndrug <- length(unique(myAllom$drug))

myALLomBIAS <- myAllom[!duplicated(myAllom$drug),]
myALLomBIAS <- myALLomBIAS[,c(1,3)]

myALLomBIAS <- myALLomBIAS
#head(myALLomBIAS)
#length(myALLomBIAS$drug)

lmmycoefficient <- c()
lmmyslope <- c()
lmpredcl <- c()

##### NEW CODE FOR RMSE and BIAS
biaslm <- c()
rmselm <- c()
rs2 <- c()
##### NEW CODE FOR RMSE and BIAS
for (i in c(1:133))
{
temp <- myAllom[myAllom$drug==i,]
```

```
myls <- lm(cl ~ wt, data = temp,method = "qr")

myPars <- coef(myls)
lmcoefficient <- replicate(length(unique(temp$species)), exp(myPars[1]))### NOTE: myPars[1]
should be changed ###
lmslope <- replicate(length(unique(temp$species)),myPars[2])
lmmycoefficient <- c(lmmycoefficient,lmcoefficient)
lmmyslope <- c(lmmyslope,lmslope)
lmpredcl <- c(lmpredcl,exp(myPars[1]) * (exp(temp$wt)^myPars[2]))

##### NEW CODE FOR RMSE and BIAS
rs2temp <- summary(myls)$r.squared
rs2 <- c(rs2,rs2temp)

lmpredtemp <- exp(myPars[1]) * (exp(temp$wt)^myPars[2])
residtemp <- lmpredtemp - exp(temp$cl)
biaslmtemp <- mean(residtemp)/mean(lmpredtemp)*100
biaslm <- c(biaslm,biaslmtemp)

nspecies <- length(temp$wt)
residtemp2 <- (lmpredtemp - exp(temp$cl))^2
rmselmtemp <- (mean(residtemp2))^0.5/mean(lmpredtemp)*100
# rmselmtemp <- ((residtemp2/mean(lmpredtemp)/(nspecies-2))^0.5)*100
rmselm <- c(rmselm,rmselmtemp)
##### NEW CODE FOR RMSE and BIAS
}

myALLomBIAS$biaslm <- biaslm
myALLomBIAS$rmselm <- rmselm
myALLomBIAS$rs2 <- rs2
```

CHAPTER 5

CONCLUSIONS AND FUTURE DIRECTIONS

Allometric scaling (AS) has been widely used in predicting human clearance (CL) based on animal CL data. Substantial prediction errors have been commonly observed in the application of this method, and various modifications to AS have been proposed in the past decades. However, none of them have provided a broad reliable improvement in prediction of human CL. There has been great controversy about how to use AS, mainly on whether to use fixed-exponent AS or varying-exponent AS. For fixed-exponent AS, researchers are also divided on which exponents and which species to use.

In this study, a nonlinear mixed effect modeling (MEM) approach was conducted on a large data set collected from the literature (number of compounds = 251), including intravenous pharmacokinetic parameter (CL) values in humans and rat or dog or monkey (at least three species including humans). The estimated central tendency and distribution of AS exponent were generally consistent with literature reports and strengthens the confidence of applying commonly accepted allometric exponents. Polar surface area (PSA) was the only covariate identified as a statistically significant covariate for the AS coefficient by explanation of 3% of inter-drug variability for AS coefficient. However, this finding may not have much practical usage to significantly affect the prediction of human CL by AS. Overall, with the largest data set reported

in the allometric field of pharmacokinetics and the rigorous analyses on the correlations of the physiochemical properties and allometric relationship, this work shows little or no impact of physiochemical covariates on the allometric predictions of clearance.

In this study, single species AS was also systemically investigated using the same data. The estimated single species AS exponents were consistent with the literature reports and the commonly used single species AS exponent values. There were no obvious correlations identified between the estimated AS exponents and the physicochemical properties or pharmacokinetic properties of the compounds. For a hypothetical compound under drug development, stochastic simulations, based on the uncertainty obtained from the data and modeling results from this work, were performed to capture the uncertainty in the predictions of human CL from single species methods. The population results obtained provided a framework in incorporating the uncertainty in allometric scaling using single species, which is recommended in real world practice.

Evaluation and cross comparison were conducted for the statistical methodologies in analyzing allometric functions, namely the log-log transformation followed by linear regression (LL-LR) and direct nonlinear regression (NLS) with different weighting schemes. The LL-LR method and the NLS with $1/CL^2$ weighting resulted in the most similar allometric exponent with central tendency around 0.668. This value is close to what has been reported in literature. In addition, these two methods provided the best predictability among the different methods, which supports the widely used LL-LR method used for pharmacokinetic interspecies scaling. Furthermore, the statistic indices, R^2, RMSE% and BIAS%, were all shown to bear poor correlations with the prediction performance. Lastly, LL-LR analysis corrected by MLP and BrW were demonstrated to be no better, or even worse, than the direct LL-LR method.

The knowledge gained from this work should contribute to a better understanding of the variability in AS exponents and better practice in performing AS in human CL prediction. The intensive data analysis with a large data set collected in this work did not indicate any physicochemical and DMPK parameters that would help to explain inter-drug variability in allometric exponent and reduce prediction errors. These results were not entirely surprising as clearance by nature is a biological process, which involves with the metabolic enzymes and/or transporters for most drugs that are not eliminated by passive excretion like renal filtration. It is well accepted that drug distribution is more likely to be impacted by the compounds physiochemical properties. For example, many reports have successfully showed the *in silico* prediction of steady-state volume of distribution (Vss) based on physiochemical properties alone. On the contrary, there are no publications or models that show reliable and acceptable prediction of clearance based on physiochemical properties. Therefore, future work, seeking to explain the allometric relationship, should focus on the parameters that reflect the biological processes. For example, the interspecies difference in the metabolic activities, such as CYPs, should be systemically investigated with regard to the *in vivo* allometric relationship. Of course, this type of data needs more intensive experimentation and literature searching and evaluation, as for each compound under investigation, the elimination routes and major metabolic pathway need to be clarified. Overall, allometry has been an empirical and useful prediction tool, and it will continue to be valuable in the field of human PK prediction. However, more mechanistic investigations, in conjunction of rigorous statistical analyses as reflected in this work, should be invested in this field.

VITA

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